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COGNITIVE PERFORMANCE AND CLINICAL FEATURES IN ADULTS WITH VULNERABILITY TO PSYCHOSIS

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ABSTRACT

Psychotic disorders are characterized by symptoms that interfere with an understanding of reality. Such symptoms consist of, for example, delusions and hallucinations. Patients suffering from psychotic disorders, particularly those with schizophrenia, often have cognitive deficits that compromise efficient information processing. Patients with schizophrenia have been found to have, in addition to a generalized cognitive deficit, deficits in attention, memory and executive functioning, which are related to the impaired psychosocial functioning typically observed in these patients. In addition to the patients themselves, non-psychotic relatives of schizophrenia patients manifest similar, although milder, deficits in cognitive functioning, suggesting that these cognitive features are related to a shared familial vulnerability. Negative symptoms such as avolition, anhedonia and blunted affect are often part of the clinical picture of schizophrenia. Anhedonia refers to a diminished ability to experience pleasure and is often elevated in patients with schizophrenia. It has been considered to be a vulnerability factor for schizophrenia.

People from the general population may also experience psychotic-like thoughts or perceptions. These are similar to those of patients suffering from psychotic disorders but milder, subclinical. Still, in adolescent and young adult samples, psychotic-like symptoms have been found to be associated with an elevated risk for future psychotic disorder.

The aim of the present thesis was to study cognitive functioning and clinical features in two middle-aged populations who presumably had a more heightened susceptibility to psychotic disorders than the general population. Samples were drawn from large population-based studies, a schizophrenia family study and The Health 2000 and 2011 studies, from The National Institute for Health and Welfare (previously National Public Health Institute). The present study aimed to explore aspects of vulnerability to psychotic disorders, first with healthy siblings of patients with schizophrenia, and then with subjects with psychotic- or manic-like experiences from the general population.

Healthy adult siblings from schizophrenia families had deficits in neuropsychological tasks that had an executive and performance speed component in comparison with population controls. The level of social and physical anhedonia, as measured with the Chapman Scales, did not differ between groups of siblings and population controls. Subjects with schizophrenia spectrum disorders (schizophrenia, schizoaffective disorder or schizophreniform disorder) had significantly poorer cognitive functioning than their unaffected siblings and controls, and also had significantly higher levels of social and physical anhedonia. Differences between middle-aged

subjects with psychotic-like or manic-like experiences and population controls were rather small. Subjects with psychotic-like or manic-like experiences had slightly lower reported level of functioning, and subjects with manic-like experiences also had more depressive symptoms. However, reported level of social and occupational functioning did not differ between the groups. No major neuropsychological differences were found. Neither psychotic-like nor manic-like experiences measured at baseline predicted conversion to psychosis during an eleven-year follow-up. Still, subjects with manic-like experiences had more non-psychotic psychiatric disorders, as well as hospital treatment for those disorders, than population controls or subjects with psychotic-like experiences at baseline.

In conclusion, among middle-aged samples, healthy siblings from families with schizophrenia have mild cognitive deficits, even in the absence of a current non-psychotic psychiatric disorder. Elevated physical or social anhedonia was not found in siblings, suggesting that elevated anhedonia is more related to the illness than familial liability in middle-aged (above peak risk age for conversion to psychosis) subjects with a familial risk for psychosis. Psychotic-like experiences in middle-aged subjects may be more benign regarding risk for future psychosis than in younger age groups, since neither psychotic-like nor manic-like experiences at baseline predicted psychosis during eleven-year follow-up. However, results should be replicated in larger study groups, and if possible, with a longer follow-up period.

TIIVISTELMÄ

Psykoosisairauksissa oireet, jotka heikentävät todellisuudentajua ovat tyypillisiä. Tällaisia oireita ovat mm. harhaluulot sekä harhanäyt. Psykoosisairauksia sairastavilla potilailla, erityisesti skitsofreniapotilailla, on usein kognitiivisia häiriöitä, jotka vaikeuttavat tehokasta tiedonkäsittelyä. Skitsofreniapotilailla on havaittu laaja-alaisen kognitiivisen heikentymän ohella vaikeuksia tarkkaavuudessa, muisti- ja toiminnanohjaustoiminnoissa. Kognitiiviset häiriöt vaikuttavat osaltaan psykososiaalisen toimintakyvyn heikentymiseen, joka on tyypillistä näillä potilailla. Myös skitsofreniapotilaiden ei-psykoottisilla sukulaisilla on havaittu samankaltaisia, joskin selvästi lievempiä, kognitiivisia vaikeuksia. Tällä perusteella on ajateltu, että kognitiivisen toiminnan piirteet liittyisivät perinnölliseen sairastumisalttiuteen. Negatiiviset oireet, kuten aloitekyvyn puute, heikentynyt kyky kokea mielihyvää sekä tunneilmaisun niukkuus ovat usein osa skitsofrenian kliinistä kuvaa. Anhedonia eli heikentynyt kyky mielihyvän kokemiseen on usein tavanomaista voimakkaampaa skitsofreniapotilailla kuin yleisväestössä. Sen on myös arvioitu liittyvän alttiuteen sairastua skitsofreniaan.

Myös yleisväestössä voi esiintyä psykoottisenkaltaisia ajatuksia tai havaintoja. Nämä ovat samankaltaisia, mutta lievempiä, kuin psykoosisairauden diagnoosin saaneilla henkilöillä. Kuitenkin nuoriso- ja nuorten aikuisten aineistoissa psykoottisenkaltaisten oireiden on todettu liittyvät kohonneeseen psykoosisairauden riskiin tulevaisuudessa.

Tässä tutkimuksessa selvitettiin kognitiivista toimintakykyä sekä psykososiaalisen toimintakyvyn piirteitä aikuisväestössä, kahdessa ryhmässä joissa oletettavasti on kohonnut alttius psykoosisairauden puhkeamiseen verrattuna yleisväestöön. Osajulkaisuissa kartoitettiin psykoosialttiuteen liittyviä piirteitä sekä skitsofreniapotilaiden terveillä sisaruksilla, että sellaisilla yleisväestön henkilöillä, jotka ovat raportoineet psykoottisenkaltaisia tai maniankaltaisia oireita. Verrokkiryhmänä käytettiin edustavaa otosta yleisväestöstä. Tutkimusaineistot ovat peräisin laajoista väestöpohjaisista tutkimuksista jotka on toteutettu Terveiden ja Hyvinvoinnin laitoksella (entinen Kansanterveyslaitos): skitsofreniaperhetutkimuksesta sekä Terveys 2000 ja Terveys 2011 – tutkimuksista.

Skitsofreniapotilaiden terveillä aikuisilla sisaruksilla todettiin lieviä puutoksia sujuvaa toiminnanohjausta ja nopeutta edellyttävissä neuropsykologisissa tehtävissä verrattuna väestökontrolleihin. Chapmanin anhedoniakyselyillä mitattu sosiaalisen ja fyysisen anhedonian määrä ei eronnut sisarusryhmien ja kontrollien välillä. Skitsofreniaspektrin häiriötä, eli skitsofreniaa, skitsoaffektiiivista tai skitsofreniformista häiriötä,

sairastavilla henkilöillä oli merkittävästi heikompi kognitiivinen suoriutuminen verrattuna terveisiin sisaruksiinsa ja kontroleihin. Heillä todettiin myös enemmän sosiaalista ja fyysistä anhedoniaa. Psykoottisen – tai maniankaltaisia oireita raportoineiden keski-ikäisten henkilöiden ja kontrollien väliset erot olivat varsin pieniä. Oireita raportoineiden henkilöiden psykososiaalinen toimintakyky oli hieman matalampi kuin kontrollien ja maniankaltaisia oireita raportoineilla oli hieman enemmän masennusoireita. Ammatillinen toimintakyky ei eronnut ryhmien kesken. Lähtötilanteessa raportoidut psykoottisenkaltaiset tai maniankaltaiset oireet eivät ennustaneet psykoosisairautta yhdentoista vuoden seurannassa. Kuitenkin maniankaltaisia oireita raportoineilla henkilöillä oli seuranta-aikana enemmän ei-psykoottista psykiatrasta sairastavuutta sekä enemmän sairaalahoitoja näihin kuin kontroleilla tai psykoottisenkaltaisia oireita raportoineilla henkilöillä.

Johtopäätöksenä, skitsofreniapotilaiden terveillä sisaruksilla voi esiintyä lieviä kognitiivisia vaikeuksia, vaikka heillä ei ole ajankohtaista ei-psykoottista psykiatrasta oireilua. Sisaruksilla ei esiintynyt sosiaalista tai fyysistä anhedoniaa enemmän kuin kontroleilla. Tämä voi viitata siihen, että voimakas anhedonia liittyy enemmän skitsofreniaspektrin sairauteen kuin perinnölliseen sairastumisalttiuteen keski-ikäisillä henkilöillä (yli keskimääräisen psykoosiin sairastumisen riski-ään). Keski-ikäisten psykoottisenkaltaiset oireet saattavat olla sairastumisriskin osalta hyvänlaatuisempia kuin nuoremmassa ikäryhmissä. Suhteellisen pienet ryhmäkoot huomioiden erityisesti sairastumisriskiä tulisi kuitenkin arvioida suuremmalla aineistolla ja/ tai pidemmällä seuranta-ajalla kuin mikä oli mahdollista tässä tutkimuksessa.

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LIST OF ORIGINAL PUBLICATIONS

The present thesis is based on the following articles, which are referred to in the text by Roman numerals (I-IV)

- I Kuha, A., Tuulio-Henriksson, A., Eerola, M., Perälä, J., Suvisaari, J., Partonen, T., Lönnqvist, J. (2007): Impaired executive performance in healthy siblings of schizophrenia patients in a population-based study. *Schizophrenia Research*, 92: 142-150

- II Kuha, A., Suvisaari, J., Perälä, J., Eerola, M., Saarni, S.S., Partonen, T., Lönnqvist, J., Tuulio-Henriksson, A. (2011): Associations of anhedonia and cognition in persons with schizophrenia spectrum disorders, their siblings and controls. *The Journal of Nervous And Mental Disease* 199 (1): 30-37

- III Wikström, A., Tuulio-Henriksson, A., Perälä, J., Saarni, S., Suvisaari, J. (2015): Psychotic-like experiences (PLE's) in middle-aged adults. *Schizophrenia Research* 169 (1-3): 313-317

- IV Wikström, A., Tuulio-Henriksson, A., Saarni, S., Suvisaari, J. (2017): Associations of psychotic-like or manic-like experiences with later psychiatric disorder: An 11-year follow-up study of middle-aged subjects. *Schizophrenia Research* 193 (2018) 465-467

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ABBREVIATIONS

ANOVA	analysis of variance
APA	American Psychiatric Association
BDI	Beck Depression Inventory
CHR	Clinical High Risk
CI	Confidence Interval
CNV	copy number variant
CVLT	California Verbal Learning Test
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4 th Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5 th Edition
GAF	Global Assessment of Functioning
GEE	generalized estimating equation
GHQ	General Health Questionnaire
fMRI	functional magnetic resonance imaging
HILMO	Finnish Hospital Discharge Register (Care Register for Health Care, Finnish: Hoitoilmoitusrekisteri)
IQ	Intelligence quotient, Finnish: älykkyyssosamäärä
OR	Odds Ratio
OPCRIT	Operational Criteria Checklist for Psychotic Illness
M-CIDI	Münich Composite International Diagnostic Interview
MLE	manic-like experiences
MRI	magnetic resonance imaging
PAS	Physical Anhedonia Scale
PET	positron emission tomography
PIF	Psychosis in Finland
PLE	psychotic-like experiences
RSAS	Revised Social Anhedonia Scale
SCID	Structured Clinical Interview for the DSM-IV
SD	Standard Deviation
SOFAS	Social and Occupational Functioning Assessment Scale
SPECT	single photon emission computed tomography
SPSS	Statistical Package for the Social Sciences
TMT	Trail Making Test
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WHO	World Health Organization
WMS-R	Wechsler Memory Scale-Revised

1 INTRODUCTION

Psychotic disorders are severe mental disorders with delusions, hallucinations and severe behavioural abnormalities that lead to a loss of contact with reality (APA, 2013). Schizophrenia is the most common psychotic disorder and is also considered to be the most severe, but psychotic symptoms are not specific to schizophrenia (APA, 2013). Symptoms in psychotic disorders can be clustered into categories which consist of: psychosis, which is also called the positive symptom dimension, alterations in drive and volition, alterations in neurocognition, such as difficulties in memory, attention and executive functioning and affective dysregulation (Van Os and Kapur, 2009). In schizophrenia, the onset is typically at a young age with subtle cognitive, motor and social dysfunction emerging first in varying, unspecific ways, progressively worsening into more severe prodromal symptoms and leading gradually to the onset of first psychotic episode (Bora et al. 2014; Addington et al. 2016). Currently, it is thought that psychosis proneness (vulnerability to psychosis) is a continuum with individual differences existing in a person's vulnerability to developing a psychotic disorder (Ingram et al. 2005; Janssen et al. 2016). Vulnerability may be due to a combined effect of personal genetic background and certain environmental stressors, and only the most susceptible would cross over the disease threshold (Binbay et al. 2012; Ortega-Alonso et al. 2017). Genetic factors play a significant role in the development of psychotic disorders (Ripke et al. 2013; Cardno and Owen, 2014). Familial vulnerability is a known risk factor for future psychosis based on studies on offspring or relatives of subjects with schizophrenia or bipolar disorder (Liu et al. 2015). Severe, acute forms of psychotic symptoms characterize disorders such as schizophrenia and psychotic bipolar disorder, but subclinical psychotic-like experiences are also present in the general population (van Os et al. 2009). These psychotic-like experiences can consist of odd behaviour, social withdrawal, anxiety, lack of feeling, magical ideation or perceptual abnormalities that are milder than in psychotic disorders (Van Os et al. 2009).

From previous studies it is known that non-psychotic family members of schizophrenia patients have mild cognitive deficits that manifest in neuropsychological tests (Tuulio-Henriksson et al. 2002). Also, among young age groups, subjects with psychotic-like experiences have often been found to have cognitive deficits which together with psychotic-like experiences have been found to predict future psychosis, at least in clinical high-risk populations (Seidman et al. 2006). The present thesis explored two adult populations with presumed risk features for psychosis with the aim of furthering the understanding of vulnerability to psychotic disorders among

middle-aged subjects in a population-based study design. In two substudies, cognitive performance and the presence of anhedonia, one of the negative symptoms in schizophrenia, are studied among healthy, non-psychotic members from families with schizophrenia. Two other substudies focus on groups of middle-aged adults with psychotic-like or manic-like experiences (PLEs or MLEs) from a population-based survey. Cognitive performance and psychosocial functioning are explored at baseline, with an eleven-year follow-up in order to study whether PLEs, MLEs or cognitive performance at baseline predict future psychosis.

1.1 Psychotic disorders

The lifetime prevalence of psychotic disorders in Finland is 3.5 per cent, and the most common psychotic disorder is schizophrenia with a lifetime prevalence of one per cent (Perälä et al. 2007). The prevalence in Finland is somewhat higher than internationally (median 0.4 per cent, Saha et al. 2005). Schizophrenia is one of the main contributors to the global burden of disease (WHO, 2008) and is among the leading causes of disability (WHO, 2008; Wittchen et al. 2011). The incidence of psychotic disorders peaks in young adulthood. The amount of suffering and distress caused by these disorders is enormous for the patients themselves as well as for their families.

Psychotic disorders are characterized by behaviours and experiences that severely interfere with the understanding of reality. Psychotic symptoms, the central features of schizophrenia and other non-affective psychoses, consist of delusions (false beliefs), hallucinations (false perceptions) and disorganization (disturbed and confused thoughts, speech or behaviour), which are called positive symptoms (Andreasen, 1984). Particularly in schizophrenia, negative symptoms are common and often prominent. Negative symptoms are functions that are normally present in healthy persons but diminished or absent in persons with schizophrenia (Andreasen, 1983). They include anhedonia, a diminished ability to experience pleasure, flattened affect, a withdrawal from social relations (even friends and family) and impoverishment of speech and thought (Andreasen, 1983; APA, 2013).

Patients with a psychotic disorder often have cognitive deficits of differing severity (van Os et al. 2008). These are most severe in schizophrenia (Whyte et al. 2005a; Tuulio-Henriksson et al. 2011) and typically milder and at least partly state dependent in bipolar disorder (Krabbendam et al. 2005; Bearden et al. 2010). Studies on relatives of patients with schizophrenia (Whyte et al. 2005b; Tuulio-Henriksson et al. 2003) and bipolar disorder (McIntosh et al. 2005; Antila et al. 2009) have

shown that they also have similar, although milder, cognitive deficits to their affected relatives, suggesting that these trait-like cognitive features relate to a shared genetic vulnerability to these disorders (Faraone et al. 2002; Gottesman et al. 2003). Manifestation of cognitive symptoms and their severity varies across individuals (Barch, 2005; Delawalla et al. 2006) but they most typically persist with relative stability over time with most deterioration occurring around the onset of psychotic symptoms (Tandon et al. 2009).

Because of the distress and suffering related to psychotic disorders, finding ways to identify those with an elevated risk for future psychosis before full onset is highly relevant. In adolescents and young adults with an elevated risk for psychosis, early psychosocial interventions and antipsychotic treatment have been found to even prevent (Preti and Cella, 2010) or at least delay the onset of psychosis (van der Gaag et al. 2013). In the event of an outbreak of a psychotic disorder, early intervention may decrease symptom severity (Bird et al. 2010) and improve the prognosis of psychosis (van der Gaag et al. 2014).

Diagnosis of a psychotic disorder is based on an assessment of the presence of specific symptoms. Due to a lack of biological tests, differential diagnosis of psychotic disorders is often difficult. Currently, the International Statistical Classification of Diseases and Related Health Problems, 10th Edition (ICD-10, WHO, 1992) and the 4th and 5th editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM, APA, 2000; 2013) are the most used classification guidelines in diagnosing schizophrenia and other psychoses.

1.1.1 Schizophrenia

Schizophrenia is characterized by delusions, hallucinations, disorganized speech and behaviour as well as negative symptoms and marked cognitive information processing deficits interfering with the ability for independent functioning, socially and occupationally (APA, 2000; APA, 2013). In schizophrenia, thinking ability, perception and emotional functioning are often fundamentally compromised. Diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV, APA, 2000) which was used in the current studies is presented in Table 1.

Table 1. Diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition¹

Criterion symptoms: two or more of the symptoms are present for a significant proportion of time during a 6-month period, or less if successfully treated	<ul style="list-style-type: none"> - Delusions - Hallucinations - Disorganized speech - Grossly disorganized or catatonic behaviour - Negative symptoms <p>Only one of the criterion symptoms is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts or two (or more) voices conversing with each other</p>
Social and occupational dysfunction	One or more major areas of functioning (work, interpersonal relations, self-care) are markedly below the level achieved prior the onset of symptoms, for a significant proportion of time
Duration	Signs of the disorder persist for at least 6 months. This period must include at least one month of symptoms that meet criterion A (active-phase symptoms, less than one month if successfully treated). Also, this 6-month period may include periods of prodromal and residual symptoms
Exclusion	<p>Schizoaffective disorder and mood disorder with psychotic features</p> <p>The disturbance is not due to a general medical condition or substance use</p>
Relationship to a pervasive developmental disorder	In case of a history of autistic disorder or another pervasive developmental disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are present for at least one month (less if successfully treated)

¹ American Psychiatric Association, 2000

Recently, the definitions of different psychotic disorders have been updated in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5, APA, 2013). Regarding schizophrenia in DSM-5, the so-called first-rank symptoms (e.g. running commentary voices, bizarre delusions, delusions of control, delusional perception, thought withdrawal, insertion or broadcasting) alone are not enough to fulfill criteria A, because evidence for first-rank symptoms as the main differentiating symptoms between schizophrenia and other psychoses is unclear (Nordgaard et al. 2008). This has additional influence on diagnostic criteria for schizoaffective,

schizophreniform and delusional disorders. In schizoaffective disorder the relationship between mood symptoms and psychotic symptoms has been clarified: symptoms which fulfil the criteria for a mood disorder need to be present for the majority of the total duration of the active and the residual portions of the illness (over 50%). In addition, DSM-5 includes a rating scale for the dimensional assessment of domains of psychopathology in psychosis, which consists of the five diagnostic criteria for schizophrenia (hallucinations, delusions, disorganized speech, abnormal psychomotor behaviour and negative symptoms) as well as dimensions of depression, mania and impaired cognition (Barch et al. 2013).

People at risk of developing schizophrenia often already show subtle cognitive, social and motor dysfunction in childhood, followed by anxiety, low mood and social withdrawal in adolescence (Addington et al. 2016; Fusar-Poli et al. 2013). These early signs may be followed by prodromal symptoms, generally leading to the onset of first psychotic episode (Howes and Murray, 2014). Prodromal symptoms disrupt daily life. These symptoms often include sleeping disturbances, depressive mood and social withdrawal as well as positive symptoms such as perceptual abnormalities (Yung et al. 2007; Brewer et al. 2005; Hafner et al. 2013). Additionally, the level of cognitive functioning may decline before manifestation of the disorder (Seidman et al. 2016). Deterioration in cognitive functioning during adolescence has been found to predict future schizophrenia or other non-affective psychoses (MacCabe et al. 2013).

The course of schizophrenia is individual, typically fluctuating with enduring residual positive and negative symptoms interspersed by acute exacerbations of positive symptoms. An essential element in treatment is antipsychotic medication for reducing psychotic symptoms and preventing relapse (Leucht et al. 2012). In addition to psychopharmacology, treatment typically includes an individually tailored combination of psychoeducation, family intervention, cognitive-behavioural therapy (Bird et al. 2010), and cognitive remediation may also be recommended (Wykes et al. 2011; Mander and Kingdon, 2015; Ventura et al. 2017). In schizophrenia, duration of the active disorder is usually longer than in other psychotic disorders, and the cognitive decline is typically more severe (APA, 2013). Younger age at onset has been found to predict poorer prognosis: more hospitalizations, negative symptoms and relapses as well as poorer social/occupational functioning (Immonen et al. 2017). Even though most subjects with schizophrenia manage to overcome the psychotic episodes with optimal treatment, cognitive, functional and emotional impairment often persist with either progressive course or more stable deficit, with only 13.5% median recovery estimate according to a recent meta-analysis (Jääskeläinen et al. 2013).

1.1.2 Schizophreniform disorder

Symptoms of schizophreniform disorder are basically identical to those of schizophrenia, with the exceptions being that the duration of symptoms is at least one month and full recovery is in 6 months. Additionally, decline in functioning is not required in the diagnostic criteria. The diagnosis of schizophreniform disorder is often provisional and if the symptoms persist over six months, the diagnosis is changed to schizophrenia (APA, 2000).

1.1.3 Schizoaffective disorder

In schizoaffective disorder, the full criteria of both the active phase of schizophrenia and a mood episode must be met. A mood episode may be a major depressive episode, manic or mixed episode. Additionally, during the same period of illness, at least a two-week period with delusions and hallucinations, but without prominent mood symptoms, should exist. In schizoaffective disorder, symptoms that meet the diagnostic criteria for a mood episode must be present for a substantial proportion of the total duration of active and residual periods (APA, 2000).

1.1.4 Mood disorders with psychotic features

Mood disorders with psychotic features, i.e. affective psychoses, have been regarded as conditions in which psychotic features may be present as an associated feature (APA, 2013). According to the American Psychiatric Association (APA, 2000; APA, 2013), bipolar I disorder is a mental disorder characterized by one or more manic or mixed episodes, usually accompanied by major depressive episodes. Psychotic symptoms can occur during manic, mixed or depressive episodes. In general, psychotic symptoms in mood disorders have been found to be associated with more severe symptomatology, worse outcome and psychosocial functioning when compared with mood disorders without psychotic symptoms (Keller et al. 2007; Matthews et al. 2009). The psychotic symptoms included in the diagnostic criteria for psychotic mood disorders are delusions or hallucinations, while, for example, disorganized behaviour is not included in this context (Hua et al. 2011; Tandon et al. 2012). Bipolar II disorder is characterized by at least one hypomanic but no manic or mixed episodes, and one major depressive episode, which can present with psychotic features (APA, 2000).

The course of illness in bipolar I disorder is typically characterized by recurrent manic and depressive episodes, often accompanied by periods of normal mood or subthreshold mood symptoms between episodes (Judd et al. 2003; Joffe et al. 2004). The disorder is usually chronic, and causes a disability on functional outcome, psychosocial factors and quality for life for the patients (Vos and Mathers, 2000; Parikh et al. 2010). Psychotic symptoms have been found to predict poorer outcome (Kendler, 2013). In a

Finnish 5-year longitudinal study, 151 patients with bipolar I or bipolar II disorder were followed in a naturalistic, secondary-care cohort reflecting current treatment era (Pallaskorpi et al. 2015). They found that at the five-year follow-up 59.8% of subjects were euthymic, and the rest were with a current episode mostly with depressive symptoms (17.9%) or with a major depressive episode (16.1%). By five years, 96% had reached full remission but most of the subjects had several recurrences. Having lifetime psychotic symptoms was predictive of shorter time to first recurrence (after reaching remission from the index episode).

Although typically a non-psychotic mental disorder, major depressive disorder may also manifest with psychotic features. The presence of psychotic symptoms has been associated with poorer outcome (Perlis, 2010; APA, 2013). In an American study with different ethnic/racial groups, depressive remission rates were worse in subjects with auditory/visual hallucinations, and paranoid ideation had a negative impact on remission (Cassano et al. 2013).

1.1.5 Other psychotic disorders

According to the American Psychiatric Association (2000), in *delusional disorder* one or more non-bizarre delusion exists at least for one month. No other prominent active phase symptoms of schizophrenia, except tactile/olfactory hallucinations (if related to delusional theme), should be present. Functioning is not markedly impaired and behaviour is not obviously odd or bizarre. *Brief psychotic disorder* refers to a sudden onset of psychotic symptoms which last at least one day but no longer than one month. Full remission and return to premorbid level of functioning should be achieved. *Psychotic disorder not otherwise specified* refers to a condition where psychotic symptoms occur but a specific diagnosis cannot be made due to inadequate or contradictory information or symptoms and otherwise do not meet full criteria for a specific psychotic disorder. In *psychosis due to substance use* prominent delusions or hallucinations are judged to be a direct physiological effect of substance (alcohol or other substance of abuse) use or withdrawal, medication or toxin exposure. In *psychosis due to a general medical condition* the essential feature is prominent hallucinations or delusions due to direct physiological effects of a general medical condition. Clear temporal association must be found between said condition and the onset of psychotic disturbance, for example, central nervous system infection, temporal lobe epilepsy and any severe medical condition requiring treatment in an intensive care unit (APA, 2000).

1.2 Aetiology of psychotic disorders

1.2.1 Genetic influence

Psychotic disorders are complex, multifactorial disorders with many gene and several environmental risk factors that have an interactive effect when they exist simultaneously in the same individual (Gottesman et al. 2003; Cardno and Owen, 2014). Both genetic disposition and environmental factors contribute to the development of psychiatric disorders (Kim and Lee, 2016; Franke et al. 2016). Family history of psychosis has been used as a measure of genetic risk, even though it is only an indirect measure (van Os et al. 2008). Still, it is considered to be a very strong risk factor for future psychosis. Approximately 10% of people with a family history of psychosis develop a psychosis themselves (Cardno and Owen, 2014; Liu et al. 2015).

Genetic vulnerability plays an important role especially in the aetiology of severe disorders such as schizophrenia and bipolar disorder (Uher, 2014; Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018). The heritability, i.e. the proportion of variance explained by genetic factors in a certain population, is estimated to be approximately 60-80% for schizophrenia (Cardno and Owen, 2014; Cardno et al. 1999; Cardno et al. 2002) and bipolar I disorder (Kieseppa et al. 2004; Song et al. 2015). Additionally, in a large Swedish population-based family study with hospital discharge register data heritability for schizophrenia was found to be 64% and for bipolar disorder 64% (Lichtenstein et al. 2009).

Since 2009, several significant findings have been made in the genetic research of schizophrenia. It has been found that so-called common variants, which are common in the population and not disease causing individually, may cumulatively lead to susceptibility to complex polygenic diseases such as schizophrenia (Cardno and Owen, 2014; Pardinas et al 2018). Recently, the Psychiatric Genomics Consortium reported altogether 179 independent associations meeting genome-wide significance that contribute to disease risk in schizophrenia (Pardinas et al. 2018).

In addition to the aforementioned polygenic common variants, very rare copy number variants (CNVs), that are present in a very small proportion of the population but have a several-fold effect on schizophrenia risk, have been identified from genome-wide association studies (Malhotra and Sebat, 2012). A recent study by the Psychiatric Genomics Consortium confirmed eight deletions or duplications to have genome-wide significant association with schizophrenia (<https://www.ncbi.nlm.nih.gov/pubmed/27869829>). While copy number variants are found only in a small fraction of patients with schizophrenia, in this population they are the strongest contributors to the pathogenesis of the disease (Stefansson et al. 2014). Also, exome and whole-genome sequencing studies have allowed the identification of first rare mutations in single genes (loss-of-function variants) which are associated

with up to a 35-fold increased risk of schizophrenia (Singh et al. 2016; Steinberg et al. 2017; Singh et al. 2017).

1.2.2 Environmental influence

Genetic vulnerability interacting with adverse environmental effects may be a pathway leading to the development of a psychotic disorder (Uher, 2014). Environmental factors can be pre- or perinatal or occur later in life (Liu et al. 2015; Walder et al. 2014). While there are several environmental factors that have been found to be associated with an increased risk for psychosis, it should be noted that in each individual different environmental exposures can precipitate and influence one another. The Vulnerability-Stress model of schizophrenia suggests that genetic factors and/or perinatal risk factors result in increased vulnerability to later environmental risk factors (Van Winkel et al. 2010). This in turn triggers psychotic symptoms if the threshold of psychosis is met (van Os et al. 2008; Tsuang et al. 2004). The progressive neurodevelopmental model suggests that schizophrenia results from abnormal brain development starting from the fetal period (Rapoport et al. 2012) and affecting brain maturation during childhood and adolescence (Nour and Howes, 2015). Table 2 presents environmental factors for which gene-environment interplay has been suggested.

Table 2. Environmental exposures for psychosis (modified from van Winkel et al, 2010)

Variables	
Fetal life	Pregnancy complications (fetal hypoxia, fetal folate deficiency) Prenatal maternal infection, stress or folate deficiency Advanced paternal age Prenatal exposure to chemical agents (e.g. lead)
Early life	Early rearing environment (institutional care, inadequate parenting) Childhood trauma (abuse, neglect)
Middle childhood/adolescence	Urban environment (level of population density, or size of a city where individual was growing up) Cannabis use Migration Stressful life events Traumatic brain injury Bullying
Wider social environment	Neighbourhood measures of social fragmentation, social capital and social deprivation
Microenvironment in daily life	Small daily life stressors (assessed with momentary assessment technology) subtly impacting affect, salience and reward

1.2.3 Brain imaging findings

Studies using neuroimaging have found structural brain alterations in patients with psychotic disorders that may have already been present at onset of psychosis (Crossley et al. 2016; Schmidt et al. 2016). Magnetic resonance imaging (MRI) is the typical technology used in these studies. However, no specific diagnostic or prognostic biomarkers that would have clinical utility have been found (Fusar-Poli and Meyer-Lindenberg, 2016). A recent meta-analysis of structural studies across several psychiatric disorders (schizophrenia, bipolar disorder, depression, anxiety, addiction and obsessive-compulsive disorder) found converging grey matter loss in the same brain areas, suggesting that diagnosis-specific effects are few and that there are shared neural substrates across psychopathology (Goodkind et al. 2015). There are also several confounding factors in interpreting the results from MRI studies in populations with psychotic disorders: in addition to the effects of chronicity of illness (severity of psychotic symptoms) or antipsychotic exposure (Huhtaniska et al. 2017), factors such as age, smoking, substance abuse and other cardiovascular risk factors can alter brain structures (Fusar-Poli and Meyer-Lindenberg, 2016).

In addition to the methods of structural neuroimaging, positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been used to investigate the nature of dopaminergic dysfunction in schizophrenia (Juckel, 2016). Based on these studies, one finding is the dysfunction of the striatal dopaminergic system that produces an increase in presynaptic synthesis of dopamine in patients with schizophrenia (Howes et al. 2012).

Studies using functional magnetic resonance imaging (fMRI) have identified abnormal activations in a wide diversity of brain regions and across different cognitive domains (Crossley et al. 2016). Compared to controls, patients with schizophrenia can have either reduced or greater activation (Callicott et al. 2000; Surguladze et al. 2006), or a combination of both (Quintana et al. 2003), depending on the task and the regions studied. In schizophrenia, functional connectivity (interactions between different brain regions) has been found to differ from that of normal subjects with task-specific under-activation accompanied by over-activation of topologically central, less functionally specialized network nodes, possibly representing a compensatory response (Crossley et al. 2016).

1.3 Negative symptoms and anhedonia

Negative symptoms such as blunted affect, alogia, asociality, avolition and anhedonia reflect a diminishment or loss of certain areas of functioning, and are often part of the clinical picture in schizophrenia (Andreasen, 1983; Lincoln et al. 2017). Negative symptoms have often received less attention in research possibly because they are less salient, less responsive to antipsychotic medication and more difficult to assess due to their relationship with other features of the disorder, such as depression, disorganization and cognitive deficits, as well as side effects of antipsychotic medication (Aleman et al. 2017). However, negative symptoms have a marked impact on social functioning and quality of life in patients with schizophrenia (Robertson et al. 2014; Fervaha et al. 2014).

Anhedonia refers to inability or diminished ability to experience pleasure (Horan et al. 2006b), and it has been considered a vulnerability factor for schizophrenia. Chapman et al. (1976) introduced distinctions between physical anhedonia (e.g. pleasure from eating, touching, smell) and social anhedonia (pleasure from being with or communicating with other people). He and colleagues developed several scales in order to measure personality traits indicating predisposition to psychosis (Chapman et al. 1994). It has been found that persons with schizophrenia have elevated levels of anhedonia both in early and later, more chronic states of the disorder (Horan et al. 2006b; Blanchard et al. 2001). Anhedonia may also be present before

the illness onset as a risk factor (Gooding et al. 2006). Some studies have found elevated levels of social (Kendler et al. 1996) and physical anhedonia (Franke et al. 1994) in first-degree relatives of schizophrenia patients suggesting a familial liability to anhedonia. However, there are also studies that found similar levels of anhedonia in relatives and controls (Erlenmeyer-Kimling et al. 1993a; Craver and Pogue-Geile, 1999). Different methodology and inclusion criteria for relatives/patients may explain inconsistent findings (Schürhoff et al. 2003).

Subclinical psychotic experiences have been found to more likely predict transition to psychosis when accompanied by social anhedonia and withdrawal (Ruhmann et al. 2010; Velthorst et al. 2012). However, there is a marked heterogeneity in manifestation of anhedonia, and not all patients with schizophrenia experience anhedonia. It has been estimated that approximately one-half of the patients have anhedonia levels within the same range that has been found in healthy subjects (Schürhoff et al. 2003). In the course of the illness, anhedonia seems to remain rather stable, regardless of fluctuation of positive psychotic symptoms and other severity features of the illness. In a 10-year follow-up, both a stable trait component as well as a more variable state component of anhedonia was found, where the state component correlated with depressive symptoms (Herbener and Harrow, 2002).

However, there are several factors which may influence the level of reported anhedonia of the patients. The experience of anhedonia may be modified by antipsychotic medication that modifies motivational salience by blocking dopamine D₂ receptors, resulting in a loss of drive, energy and motivation, apathy and anhedonia (Juckel, 2016). This is most evident with the so-called typical antipsychotics (first-generation antipsychotics), while the new atypical or second-generation antipsychotics only partially block D₂ receptors (Meltzer, 2013; Juckel, 2016).

Additionally, the methods used in assessing anhedonia may vary. In clinical tradition, anhedonia has often been evaluated based on the nature of the stimulus (e.g. source of pleasure). An inability to experience pleasure from physical sources (physical anhedonia) and an inability to experience pleasure from social sources/interactions (social anhedonia) are considered to be separate domains (Wolf, 2006). When assessed using self-report questionnaires, patients with schizophrenia on average reported diminished pleasure from both social and physical sources. Despite this there was no strong correlation between physical and social anhedonia (approximately .05) (Katsanis et al. 1990) suggesting substantial independence between these domains. Gender and education have also been found to have an effect on the amount of anhedonia reported using the Chapman Scales, with men scoring higher in physical and social anhedonia (Miettunen and

Jääskeläinen, 2010) and subjects with lower education scoring higher in all the scales (Miettunen et al. 2010).

Research has tried to distinguish different types of anhedonia according to the degree of immediacy between the presented stimulus and the experience of pleasure (Cohen et al. 2012). Anticipatory pleasure (“I will enjoy it”), remembered (“I enjoyed it”) and trait pleasure (“I usually enjoy it”) are hedonic experiences removed from the time of the stimulus (Wolf, 2006; Gard et al. 2007). Judgements of anticipatory, remembered and trait pleasure and the emotional experience associated with these judgements are typically measured with either self-report or interview-rated questionnaires (Blanchard and Cohen, 2006; Horan et al. 2008a). They require effective enough cognitive processes, including memory, insight, generalization and prediction, that are often impaired in schizophrenia (Horan et al. 2006a). On the other hand, consummatory pleasure occurs immediately at the time of the stimulus with automatic emotional response representing “in the moment” or state emotional experience (Cohen et al. 2012; Cohen and Minor, 2010). Studies with self-report scales designed to separately assess anticipatory and consummatory pleasure have found that patients with schizophrenia reported more anhedonia only in relation to anticipatory items (Gard et al. 2007). Examinations of in the moment or state emotions under laboratory conditions have found that individuals with schizophrenia report experiencing normal levels of pleasant emotions (Kring and Moran, 2008; Cohen et al. 2011). It has also been found that schizophrenia patients are able to differentiate a loss of emotion from depressive mood (Dollfus and Lyne, 2016). Advances in neuroscience have identified distinct neural pathways related to the experience of anticipatory pleasure and consummatory pleasure (Cohen et al. 2011). Additionally, dopamine has been shown to be strongly linked to anticipatory rather than consummatory pleasure (Berridge, 2007) while the experience of consummatory pleasure has been linked to serotonin and opioid systems (Schulze-Rauschenbach et al. 2015; Wise, 2002).

1.4 Psychotic-like symptoms

1.4.1 Psychotic-like experiences in the general population

Psychotic-like thoughts or perceptions are not present only among people with psychotic illnesses or with people about to convert to one. People from the general population may also experience psychotic-like experiences (PLEs), such as paranoid thinking or abnormal perceptual experiences, that are qualitatively similar but milder than the experiences of patients with a diagnosed psychotic disorder (Linscott and van Os, 2013). PLEs may be bizarre, cause distress, draw attention or prompt help-seeking, but not

necessarily. They comprise phenomena which may be interpreted as clinically relevant symptoms or as subclinical, below a threshold of clinical relevance (van Os et al. 2008; Linscott and van Os, 2013). Several large population studies indicate that PLEs can be measured in the general population and that they most likely represent the behavioural manifestation of distributed multifactorial (genetic and non-genetic) risk for psychosis (van Os and Reininghaus, 2016), supporting the continuum view of psychosis. Subclinical psychotic-like experiences are rather common in the general population with a median annual prevalence at about 7% (Linscott and van Os, 2013), which is greater than the 3% prevalence of psychotic disorders (Perälä et al. 2007). In general, PLEs are transitory in most of the cases (about 80%), but around 20% develop persistent psychotic experiences and 7% of those a psychotic disorder with an annual transition rate below 1% (Linscott and van Os, 2013; Kaymaz et al. 2012).

1.4.2 PLEs and risk for future psychosis

Psychotic-like symptoms have been found to be associated with an elevated risk for future psychotic disorders (Dominguez et al. 2011; Werbeloff et al. 2012), as well as for depression and anxiety disorders (Wigman et al. 2012). However, this has mostly been studied in adolescents and young adults with clinical populations in Clinical High Risk (CHR) settings (Murray and Jones, 2012; Fusar-Poli et al. 2013a). The basic concepts of psychosis risk research are presented in Table 3.

Table 3. Definitions of concepts in psychosis risk research

Concept	Definition
Psychosis risk	Heightened risk for psychosis due to symptomatic (clinical) risk or familial (genetic) risk
Psychosis-like symptoms or experiences	Attenuated positive symptoms not severe enough to reach psychotic threshold
Prodrome	Symptomatic phase before onset of a full psychosis. A retrospective concept
Basic symptoms	Early prodromal phase with subtle, self-experienced anomalies in cognition and perception
Clinical high-risk syndrome	Symptomatic approach in psychosis risk research. Consists of: <ul style="list-style-type: none"> - attenuated positive symptoms or - brief limited intermittent psychotic symptoms or - lowered functioning with schizotypal personality or familial risk to psychosis
Familial (genetic) high risk	Family history of psychosis

CHR is a prospective concept which aims to predict the risk of transition to psychosis by clinically significant risk symptoms (Fusar-Poli et al. 2013; Addington and Heinssen, 2012). To be classified as having a clinical high risk (CHR) for psychosis, one or more of the risk criteria needs to be fulfilled: subject has attenuated psychotic symptoms, brief limited intermittent psychotic symptoms, and/or genetic risk and deterioration of functioning (Yung and McGorry, 1996; Fusar-Poli et al. 2016). Additionally, a comparably high risk for psychosis has been independently associated with an earlier phase of prodromal psychosis (Fusar-Poli et al. 2013). The concept of CHR is used in both academic studies and clinical practice to help identify adolescents and young adults at risk for future psychotic disorders (Yung et al. 2012; Fusar-Poli et al. 2013). Among individuals aged 12-35 years with a recent onset of CHR symptoms, 20-35% go on to develop a full psychotic disorder over a 2-year period (Fusar-Poli et al. 2012; Cannon et al. 2016). While the concept of a prodrome refers to the symptomatic period before full onset of first psychotic episode, CHR does not predetermine future psychosis, as the possible risk symptoms may resolve spontaneously or with early psychiatric intervention (Fusar-Poli et al. 2012; Cannon et al. 2007).

The impact that different CHR symptoms have for the transition to psychosis has been found to vary. In a recent meta-analysis, a subgroup of subjects having brief limited intermittent psychotic symptoms were found to have a higher risk for psychosis than those with attenuated psychotic

symptoms (Fusar-Poli et al. 2016). In this meta-analysis, the familial risk and deterioration subgroups were not found to have an enhanced risk for psychosis. However, it has been suggested that the impact of familial (indicative of genetic) risk might only be evident in a longer follow-up and after the age of 20 years (Rasic et al. 2014), warranting long follow-up periods of risk subjects.

The prevalence of self-reported PLEs declines between ages of 20 and 40 (Rossler et al. 2007). This may suggest true variation, or partly reflect the fact that those adolescents with PLEs indicative of future psychosis have already developed an illness. Additionally, with increasing age, understanding of the items in questionnaires for PLEs may increase and thus decrease the false positive answers (Therman et al. 2014).

Most of the studies on the significance of PLEs for future psychosis have been conducted in clinical settings. However, there has arisen an interest on PLEs in non-help-seeking general populations (van Os and Reininghaus, 2016). Among subjects with PLEs, with and without need of care, deficits in cognitive processing and ways to appraise and respond to PLEs have been found to differ between patients with psychotic disorders, those with a heightened risk for a psychotic disorder and non-help-seeking (non-clinical) group (Peters et al. 2016). Help-seeking and need of care were found to be more commonly associated with perceived cognitive symptoms, such as inability to concentrate and loss of automaticity of thinking skills, even though the reported PLEs were similar to those reported by persons without the need of care (Brett et al. 2015). Predictors of high distress relating to PLEs were changes in awareness and cognitive processes, appraisals of experiences being caused by other people and greater attempted control over experiences, while predictors of lower distress were “spiritual” appraisals of experiences, greater perceived social support and understanding, greater perceived controllability and neutral response as a reaction to PLEs (Brett et al. 2014).

In comparison to patients with psychosis, persons with persistent psychotic experiences but without need of care have been found to have greater cognitive resources (self-report of subjective difficulties), to be less socially disadvantaged and also to have more socially valued roles (Peters et al. 2016). This suggests that a lack of social and environmental adversity and good enough cognitive functioning may be protective against malign outcomes of psychotic experiences. These findings also support models in which environmental and psychological factors interact with biological processes in the aetiology of psychosis. Interestingly, cognitive behavioural therapy, which has been found to be useful to patients with psychosis, aims at decreasing distress by modifying the patient’s beliefs concerning their anomalous experiences (Mander and Kingdon, 2015).

1.4.3 Manic-like experiences

Finding means for the early detection of psychotic disorders, particularly schizophrenia, has been studied since the 1990s. Recently, interest has arisen on subthreshold manic-like experiences (MLEs) or manic-like affective symptoms, which do not fulfil criteria of bipolar disorder or other affective psychoses as predictors for these illnesses in the future (Bechdolf et al. 2014). Clinical studies have revealed a pattern of symptoms preceding the onset of bipolar disorder, of which mood lability and/or mood swings and/or cyclothymic features, depressive mood, racing thoughts, irritability and physical agitation are most commonly reported (Skjelstad et al. 2010; Howes and Falkenberg, 2011; Bechdolf et al. 2012). Early intervention has been found to lessen the severity, prevent progression and potentially delay or even prevent the onset of full-blown bipolar disorder (Correll et al. 2007; Salvatore et al. 2008). In previous studies that have used the Hypomanic Personality Scale (Eckblad and Chapman, 1986), it has been found that the scale predicted bipolar disorder and major depressive episodes (Kwapil et al. 2000) and psychosis (Miettunen et al. 2011) in young adults. It has been suggested that subthreshold affective symptoms and substance use disorders predict bipolar disorder among help-seeking young people in a 12-month follow-up (Ratheesh et al. 2015b), but there are only few studies that have addressed this and no established tools to identify individuals at risk for developing bipolar disorder (Bechdolf et al. 2014).

1.4.4 Assessment of psychotic- or manic-like experiences

Variations in assessment methodology and populations under study (particularly clinical vs. general population) are notable limitations in making direct comparisons on findings of PLEs or manic-like experiences. Presently, several psychological and psychiatric instruments are used for identifying subjects with different psychiatric disorders, as well as for recognizing those at risk for future disorders (APA, 2000; Miettunen et al. 2011; Ratheesh et al. 2015a). The methods used for assessing psychotic experiences also seem to affect the prevalence estimates, with higher prevalence found in studies using self-report methods than in those using interview-based methods (van Os, 2016). Additionally, response frequencies for different items probing PLEs may vary considerably even in general population samples, raising doubts about using a single summary score of the PLE questionnaires (Therman, 2013). In a population-based sample of Swedish women over 41 years of age, response frequencies to “positive” (indicative of PLE) items on the used measure of PLEs, the Community Assessment of Psychic Experiences, varied from 0.5% (voices conversing) to over 50% (false appearances and telepathy) (Therman, 2013).

Cultural differences and possibly socioeconomic factors may contribute to the way people understand the questions and the situation when these

experiences are measured. There is evidence that the prevalence of PLEs reported by people varies across countries (Nuevo et al. 2012). Higher lifetime prevalence estimates have been found in middle- and high-income countries than in low-income countries (McGrath et al. 2015), as well as findings that psychotic-like experiences are more common in ethnic minority groups (Linscott and van Os, 2013a; Morgan et al. 2009).

1.5 Neuropsychology and the measurement of cognition

1.5.1 Neuropsychological assessment

Cognitive domains can be assessed with neuropsychological tests that are standardized measures targeted for different aspects of cognitive processes (Andrewes, 2016). When deficits in cognitive processing are assessed in clinical practice, some formation of normal or prior level of functioning of each patient must be achieved in order to evaluate the possible change in patient's performance (Lezak et al. 2004; Lezak et al. 2012). This level, *the comparison standard*, may be *normative* (derived from appropriate population) or *individual* (derived from patient's history or present characteristics). Performance in different tests also varies relating to age, gender, education level and general mental ability as well as cultural background, in addition to possible brain pathologies or conditions affecting the efficiency of brain functioning, such as depression, anxiety or other psychiatric conditions (Lezak et al. 2004). In clinical neuropsychological assessment, both normative and individual comparison standards are used, as appropriate for the function or activity being examined and the purpose of the examination.

In research settings, the use of reliable and validated assessment methods of cognition is equally important. Additionally, it is important to use control groups that are of the same age and are recruited and tested with similar methods and at the same time as the study subjects (Snitz et al. 2006).

1.5.2 Cognitive domains and cognition as a functional system

Generally, within each class of cognitive function a division may be made between functions that mediate verbal/symbolic information and those that deal with information that cannot be communicated with words or symbols, such as complex visual or sound patterns. Even though different cognitive functions can be conceptually distinguished, it is important to note that they are interdependent and inextricably bound together. Different subclasses of functions do differ from one other in their neuroanatomical organization and in their behavioural expression, but at the same time share other basic neuroanatomical and psychometrically measurable relationships within the functional system (Andrewes, 2016; Lezak et al. 2004). Cognitive domains

are shortly presented below. The domains relevant to this study are described in more detail.

1.5.2.1 Perception

Perception includes the analysis of senses such as vision, audition, taste, olfaction (smell) and tactile and other somatosensory stimulation. It is differentiated from sensation (product of environmental stimulation prior to its perceptual interpretation). Perception is a process comprising successive and interactive stages. Those dealing with the simplest physical or sensory characteristics (colour, shape, tone) come first and form the foundation for more complex, higher levels of (e.g. semantic and visuoconceptual) processing that integrate sensory stimuli with one another and successively with past experiences, hence forming meaningful representations of things (Andrewes, 2016). Normal perception is a complex process involving many different aspects of brain function. Because of extensive cortical distribution and complexity, perceptual functions are vulnerable to damage, and depending on the location of an injury a wide range of impairments may occur (Lezak et al. 2012; Andrewes, 2016).

1.5.2.2 Attention

Attention refers to a group of brain structures and their biochemical substrates that act together in an integrated way to achieve an attentional goal (Andrewes, 2016). They can be described as the *arousal system* for maintaining suitable cortical tone/vigilance according to environmental demand; *orientation system* for detecting and orienting attention towards novel/unpredictable stimuli; *selective attention* that allows focus on one task and/or stimuli while ignoring others (at the expense of others) and an *executive attentional system* which serves to control attention by inhibiting and disinhibiting orientation responses and controlling selective attentional system (Andrewes, 2016; Buschman and Kastner, 2015). Attention can be switched, allowing focus on different tasks in quick succession in order to maintain more than one task within a similar period of time. Attention and most importantly deficits in attentional systems influence the efficiency of other cognitive functions (Lezak et al. 2012; Andrewes, 2016). Attentional systems are based on integrated activation on broad areas and connections of the brain. Particularly fronto-parietal network and thalamo-cortical interactions have crucial roles in attention, but it should be noted that the nature of attentional processing is distributed throughout the brain and sensitive to disturbance or damage (Andrewes, 2016; Dickinson et al. 2007; Buschman and Kastner, 2015)

1.5.2.3 Executive functions

Executive functions refer to a broad network in the brain that has a governing, modifying and directing role with all other cognitive functions. The highest demands for executive functions are in novel or complex situations requiring initiative (Andrewes, 2016). They require self-initiated flexible planning and organization of novel activities towards a self-generated goal. Even in simple tasks executive functions are active in selecting, maintaining and monitoring subprocesses relevant to the task at hand while inhibiting irrelevant stimuli. *Performance speed* is often affected by executive deficits (Dickinson et al. 2007). Executive functions have traditionally been associated with prefrontal cortex and the anterior cingulate cortex, but parietal and temporal cortices also play a role, as well as the important connections with subcortical areas and the cerebellum. Damage to any of these areas or tracts connecting them may lead to executive deficits (Lezak et al. 2012; Andrewes, 2016).

1.5.2.4 Memory and learning

Memory is a complex function and part of the complexity is due to the influence of other areas of cognition: impairment can happen due to perceptual, attentional, verbal comprehension, executive or motor dysfunction. *Short-term memory* refers to a simple temporary storage of information (Baddeley, 2012). *Working memory* as a concept refers to a cognitive function which combines temporary storage with conscious inspection and manipulation of information. Efficient working memory functioning requires attentional and executive resources. Working memory is essential in learning new material and closely allied to attention (Baddeley, 2012; Andrewes, 2016). Intact working memory functioning relies on dopaminergic regulation of neuronal networks, especially in the prefrontal cortex (Goldman-Rakic, 1999; Ziermans, 2013). *Long-term memory store* contains more permanent memories. *Consolidation system* is the mechanism by which information is made more permanent within long-term memory store. *Learning* new information that is momentarily maintained in working memory may require modification of long-term memory store in a purposeful process involving rehearsal and refreshing of the material, which is closely tied with both attention and executive functions (focusing and initiative in strategy formation). Consolidation system also has a role in *retrieval* of information from the long-term memory store. The consolidation system is represented by several brain structures: one of the most central being hippocampus but also other structures connected to hippocampus (e.g. the thalamus) are crucial for storing new memories (Andrewes, 2016). Most of the memory research has been focused on the *declarative memory* referring to the ability to learn about and to be able to remember facts, objects and events (Lezak et al. 2012).

1.5.2.5 Expressive functions

Expressive functions refer to means through which information can be communicated or acted upon, such as speaking, drawing or writing, gestures or movements. Deficits in language, constructional or spatial imaging abilities or motor impairment may affect these in addition to deficits in executive functioning (Andrewes, 2016).

1.6 Cognitive deficits in study populations

1.6.1 Patients with psychotic disorders

Cognitive deficits compromising efficient information processing are typical among subjects with psychotic disorders (van Os et al. 2008), and there are findings indicative of associations of memory deficit and psychosis susceptibility in general (McIntosh et al. 2005; Dominguez et al. 2009). The most severe deficits in cognition are found among patients with schizophrenia (Tuulio-Henriksson et al. 2011). In schizophrenia, a generalized cognitive dysfunction is one of the core features of the disorder, against which deficits in attention, executive functions and memory are emphasized (Dickinson et al. 2004). In most cases cognitive deficits seem to remain relatively stable or not deteriorate significantly over time (Heaton et al. 2001; Kurtz, 2005). In a Finnish longitudinal general population cohort study, the change in several dimensions of verbal learning and memory in a nine-year follow-up was compared in subjects with schizophrenia and in non-psychotic controls at midlife. Even though the subjects with schizophrenia had poorer performance than the controls in several measures of verbal learning and memory (both at baseline and at follow-up), there was no major difference in the amount of change during the 9-year follow-up (Rannikko et al. 2015a). A possible modifying factor affecting cognitive functioning in subjects with schizophrenia, in addition of the illness itself, is antipsychotic medication, especially with high doses or polypharmacy (Torniainen et al. 2012; Ho et al. 2011) as well as with higher cumulative lifetime antipsychotic dose (Husa et al. 2017). In subjects with other non-affective psychoses, deficits in verbal memory and processing speed have been found, but these were milder than with subjects with schizophrenia (Tuulio-Henriksson et al. 2011). In a population-based study on subjects with schizoaffective disorder, it was found that subjects with schizoaffective disorder also had a generalized cognitive deficit when compared to control subjects, but they outperformed subjects with schizophrenia in verbal ability, processing speed, visual working memory and verbal memory (Torniainen et al. 2012).

Cognitive deficits have been found to be already present at premorbid and prodromal phases of psychotic illness (Erlenmeyer-Kimling et al. 2000; Bora et al. 2014). Several studies have examined the clinical course of cognitive functioning in help-seeking subjects with prodromal symptoms. In meta-analyses it has been found that at-risk individuals manifest similar, albeit milder, cognitive deficits to subjects with first-episode and chronic schizophrenia, with individuals who transition to psychosis presenting with more severe deficits at intake (Fusar-Poli et al. 2012; Giuliano et al. 2012). Cognitive decline usually occurs prior and during the onset of illness (Hoff et al. 2005). In a review, global cognitive dysfunction was shown to be already present in patients with first-episode psychosis with largest effect sizes for verbal memory, executive function and general IQ (Aas et al. 2014). Cognitive deficits are also found to be present among antipsychotic-naïve patients (Fatouros-Bergman et al. 2014).

Despite changes in assessment instruments and alterations in diagnostic criteria, generalized cognitive dysfunction in schizophrenia has been robustly demonstrated over time (Reichenberg 2010). In a large meta-analytic review, the region of the world in which the cognitive functioning of schizophrenia patients had been studied had only little impact on the effect sizes reported, despite substantial geographic, cultural and linguistic differences present in these groups of subjects (Schaefer et al. 2013).

Deficits in cognition have also been found in subjects with bipolar disorder and other affective psychoses, but these are usually less severe (McIntosh et al. 2005; Trotta et al. 2015; Antila et al. 2007) and especially with bipolar disorder, partly state dependent (Krabbendam et al. 2005; Bearden et al. 2001). Medium effect size differences in cognitive domains of executive function, memory and mental speed seem to separate schizophrenia from bipolar disorder, with patients with schizophrenia having more severe deficits (Bora et al. 2009). In a recent meta-analysis, executive dysfunction was widespread in euthymic patients with bipolar disorder (Mann-Wrobel et al. 2011), and previous meta-analyses have also shown deficits in attention and verbal memory (Bora et al. 2009; Torres et al. 2010). Mixed affective and psychotic features are also part of the clinical picture of some of the patients with schizophrenia, and depression is commonly observed in schizophrenia (Kempf et al. 2005). Regardless of diagnosis, subjects with mixed psychotic and mood symptoms can have similar, although milder, cognitive deficits to those observed in subjects with schizophrenia with severe negative symptoms (Bora et al. 2009).

1.6.2 Early course of cognitive deficits

Birth cohort and conscript studies have shown that subjects who later develop schizophrenia often have early cognitive deficits, suggesting that cognitive features are partly primary and not only secondary to psychotic symptoms (Tiihonen et al. 2005; Koenen et al. 2009; Dickinson, 2014). It has been found that subjects with later schizophrenia have small to medium deficits across general and specific cognitive domains (Mollon and Reichenberg, 2018). A similar type of cognitive profile has also been found in other non-affective psychoses (Kendler et al. 2016), but less consistently in bipolar disorder (Trotta et al. 2015) and affective psychoses (Agnew-Blais et al. 2015). Hence, aberrant neurodevelopmental processes may not be specific to schizophrenia, and despite evidence for genetic overlap between schizophrenia and bipolar disorder as well as major depression (Cross-Disorder Group of the Psychiatric Genomics Consortium et al. 2013), different profiles of premorbid cognitive functioning may suggest distinct neurodevelopmental processes (Mollon and Reichenberg, 2018).

In a recent meta-analysis it was found that persons who subsequently developed schizophrenia had below average IQ at the age of 13 as well as below average motor functioning at age 16, but no differences were found in their general academic and mathematical achievement compared to those who did not develop the disorder (Dickson et al. 2012). On the other hand, it has been found that those who later develop bipolar disorder may even have above average cognitive performance (MacCabe et al. 2013; Vreeker et al. 2016). In a longitudinal study on population-based cohorts of adolescent boys and young men in Sweden (MacCabe et al. 2013), a decline in verbal ability score between ages 13 and 18 years was the strongest predictor for schizophrenia in adulthood. The results remained when adjusted for possible confounders such as urbanity, parental education or family history of psychosis. The decline in verbal ability between ages 13 and 18 was also the strongest predictor for other non-affective psychoses, but in this case a family history of psychosis also emerged as a significant predictor. In the same cohort, individuals who later developed bipolar disorder outperformed population norms on all tasks at all time points.

In the Philadelphia Neurodevelopmental Cohort Study, Gur and colleagues found that youths (between 8-21 years) who reported psychotic symptoms had a cognitive age that was behind chronological age compared to typically developed youths. Also, those with more significant psychiatric symptoms showed greater developmental lag (Gur et al. 2014). The developmental lag was found to be more pronounced in some cognitive domains: complex cognition including verbal reasoning was delayed in the psychotic symptoms group as early as at age 8 and remained delayed. Additionally, a lag in social cognition was already detectable at that age. The New Zealand longitudinal cohort study also suggests that children who later

develop schizophrenia may already have below average verbal reasoning in childhood, after which cognitive dysfunction may also manifest in working memory, attention and processing speed functions (Reichenberg, 2010; Reichenberg et al. 2002). In a group of patients with schizophrenia from Finnish longitudinal general population cohort study, , lower premorbid school marks at age 16 and lower education at age 34 predicted more cognitive decline at 43 years of age than severity of illness at first episode or later course of schizophrenia, supporting the neurodevelopmental course of development of schizophrenia (Rannikko et al. 2015b).

1.6.3 Relatives of patients with psychotic disorders

Subtle cognitive deficits have been found in relatives of schizophrenia patients, even though they do not have a psychotic disorder themselves (Snitz et al. 2006; Cannon et al. 2000; Tuulio-Henriksson et al. 2003). These findings suggest that cognitive deficits are markers of familial transmission of liability to psychosis (Gottesman et al. 2003; Faraone et al. 2000).

Level of dysfunction may be associated with familial loading, since in families with multiple affected individuals, cognitive deficits found in relatives are more pronounced than in families with only one affected individual (Tuulio-Henriksson et al. 2003; Faraone et al. 2000). In meta-analyses, the largest differences between relatives of schizophrenia patients and controls have been found in verbal learning and executive functioning (Snitz et al. 2006; Sitskoorn et al. 2004). However, at least partly due to differences in methodology and study samples, the findings concerning executive functioning have been somewhat inconsistent (Laurent et al. 2000).

Among non-psychotic relatives of patients with bipolar disorder some very mild deficits have been found, most consistently in executive functions and performance speed (Antila et al. 2007; Mur et al. 2007; Bearden et al. 2011; Antila et al. 2011). In a relatively recent meta-analysis it was found that cognitive deficits are evident in young relatives of patients with psychosis in general (non-affective or affective), even though they might be modestly more severe in relatives of schizophrenia patients (Bora et al. 2014).

There are several possible confounding factors in studies on neuropsychological performance in families with schizophrenia or affective psychosis, such as the use of different samples of relatives (for example, parents, siblings or offspring) (Egan et al. 2001), including siblings with non-psychotic illnesses of schizophrenia spectrum (Snitz et al. 2006) or groups of relatives with mean age under the average risk for psychosis (Heydebrand, 2006). In addition, sensitivity of the neuropsychological methods used in studies may vary, explaining some inconsistency in results (Trandafir et al. 2006).

1.6.4 Shared genetic aetiology between cognition and schizophrenia

When studying subjects with a familial susceptibility to psychosis, there are several confounding factors to the effects of shared genetic features of patients and their relatives. Rearing environment in families with schizophrenia may not be optimal. Offspring of parents with a psychotic disorder may be more exposed to stress and inadequate parental care (Walder et al. 2014; Campbell et al. 2018) as well as socioeconomic difficulties (Howard et al. 2004) than in families without a psychotic disorder.

Recently, with advances in genetic technology and analytic approaches, it has been possible to study the extent to which cognitive ability and schizophrenia share genetic aetiology in subjects with common genetic variants associated with schizophrenia (Hubbard et al. 2016). The proportion of phenotypic correlation between cognition and schizophrenia due to shared genetic effects has even been found to be 21-56% in some twin studies (Toulopoulou et al. 2007; Toulopoulou et al. 2010), but in a population-based twin study only 7% of the genetic variance for psychosis was shared with cognition (Fowler et al. 2012). In population samples, increased polygenic risk score of schizophrenia has been found to be weakly associated with lower general cognitive ability (McIntosh et al. 2013; Lencz et al. 2014). In an Icelandic study of a large genotyped sample of CNV control carriers (subjects with CNVs but without manifest disease), cognitive performance of carriers was found to be at a level between that of schizophrenia patients and of population controls who were not carriers (Stefansson et al. 2014). Since CNVs are not fully penetrant to the disease their effect on cognition of the carriers can be studied separately from that of the manifest disease.

1.6.5 Anhedonia and cognitive dysfunction in schizophrenia

Negative symptoms, anhedonia among them, have been found to associate with deficits in a variety of cognitive domains in schizophrenia (Szendy et al. 2006; Winograd-Gurvich et al. 2006). In a meta-analysis on cognitive functioning in schizophrenia, schizoaffective disorder and affective psychosis, people with schizophrenia performed worse than those with schizoaffective disorder or affective psychosis, but the effect sizes were small and with substantial heterogeneity of distribution (Bora et al. 2009b). More severe deficits in memory, psychomotor speed and executive function were associated with greater severity of negative symptoms in schizophrenia subjects (Bora et al. 2009b).

Anhedonia itself has been found to correlate significantly with generalized cognitive dysfunction in schizophrenia patients and moderate relationships between anhedonia and measures of executive functioning and visual memory functions have been found both among schizophrenia

patients and their unaffected relatives (Franke et al. 1994; Laurent et al. 2000). Particularly physical anhedonia has been found to correlate with cognitive functioning in subjects with psychotic disorders (Brose and Woodward, 2015).

In a community sample of young subjects, those with elevated social anhedonia have been found to perform poorer than controls in tasks measuring visual memory and visual-spatial construction (Cohen et al. 2006). Additionally, higher levels of anhedonia have been found to be related to deficits in emotion perception in both subjects with schizophrenia and controls (Herbener et al. 2008).

1.6.6 Cognitive deficits in subjects with PLEs.

Neuropsychological functioning in subjects with PLEs has mostly been studied within clinical settings in young or adolescent subjects in Clinical High Risk (CHR) studies. In CHR subjects, psychotic-like symptoms have been associated with lower working memory capacity (Ziermans, 2013) as well as with impaired performance in a visuospatial task (Lindgren et al. 2010). Neuropsychological deficits have been found to predict psychosis in several CHR samples (Keefe et al, 2006; Wood et al, 2007; Cannon et al. 2016). In a follow-up study, those CHR subjects who progressed to psychosis had more severe cognitive deficits, while those at-risk subjects who did not convert to psychosis did not differ significantly from controls (Keefe et al, 2006). In a recent large multicentre study, high-risk subjects were found to have deficits in attention, working memory and declarative memory, with most severe deficits in subjects who later developed psychosis (Seidman et al. 2016). In a study from North American Prodrome Longitudinal Study on predictors for psychosis in CHR subjects, higher levels of unusual thought content and suspiciousness, greater decline in social functioning, lower verbal learning and memory performance, slower speed of processing and younger age at baseline each contributed to individual risk for psychosis (Cannon et al. 2016).

It has been suggested that the effects of genetic risk and clinical status on cognitive function are independent in CHR subjects, and that cognitive deficits associated with early psychosis are genetically mediated and can occur in genetically vulnerable individuals regardless of their clinical status (Myles-Worsley et al, 2007). In a recent meta-analysis on young subjects (mean age from 15 to 29), it was found that co-occurrence of both familial and clinical risk associated with more severe cognitive dysfunction (Bora et al. 2014). In the same study, it was also found that the CHR subjects who developed psychotic disorders at follow-up had more severe cognitive deficits at baseline with effect sizes varying (between $d=0.31-0.49$) on all cognitive domains except sustained attention. There was a significant overlap of baseline cognitive performance of the clinical high-risk subjects who did or

did not develop psychosis. Hence, cognitive deficits may have only a limited capacity to predict the outcome of high-risk patients (Bora et al. 2014).

Outside clinical settings with help-seeking subjects, research is scarce. The available studies with non-help-seeking CHR individuals suggest that they have less cognitive deficits (Mukkala et al. 2011). Older subjects with PLEs have not been thoroughly studied possibly because they are above the risk age for conversion to psychosis (Fusar-Poli et al. 2014).

1.7 Motivation for the current studies

Middle-aged subjects with vulnerability to psychosis have received less attention than adolescents or young adults, understandably since psychotic disorders most often develop at young age. However, considering the importance of understanding risk features for psychosis and their manifestation in different age groups, after average risk age of onset of a psychotic disorder, exploring older subjects with presumable risk to psychosis is relevant. The present thesis focuses on two adult populations with either familial or clinical risk for psychosis. Cognitive functioning in these groups is explored, as well as whether psychotic-like symptoms in middle-aged subjects predict future psychosis. The aim is to have more understanding on the way cognitive functioning and clinical symptoms relating to vulnerability to psychotic illness manifest in these populations.

2 AIMS OF THE PRESENT STUDIES

The present thesis focuses on two middle-aged populations who presumably have a higher risk for psychotic disorders than the general population:

- 1) siblings of patients with schizophrenia
- 2) adults with psychotic-like symptoms

The specific aims of the study were:

- I) To explore differences in cognitive performance between healthy siblings of schizophrenia patients and a representative, population-based control group (Study I)
- II) To find out whether levels of social and physical anhedonia differ between subjects with schizophrenia spectrum disorders and their unaffected siblings with a population-based control group and to explore associations of physical and social anhedonia with cognitive performance (Study II)
- III) To explore cognitive performance and psychosocial functioning of subjects with psychotic-like or manic-like experiences (PLEs or MLEs) in comparison with control subjects in a sample of middle-aged adults from a general population survey (Study III)
- IV) To study, using the same population-based sample as in Study III, whether PLEs, MLEs or cognitive performance at baseline predict psychosis or other psychiatric disorders at eleven-year follow-up (Study IV).

3 METHOD

3.1 Two population samples

Samples for studies in this thesis were drawn from two large population-based samples of subjects, with a focus on subjects with different vulnerability features relating to possible susceptibility to psychosis and population controls without such features. Studies I and II are based on a large sample of families with at least two siblings with schizophrenia and their first-degree relatives from Finland, with control subjects from the Health 2000 study, a representative national health examination survey. Studies III and IV are based on the Health 2000 Study sample, with Study IV also including data from the Health 2011 study, which is a follow-up study of the Health 2000 study sample.

3.1.1 Schizophrenia family data

A large population-based sample of families with schizophrenia was recruited for studying the genetic epidemiology and molecular genetics of schizophrenia from the beginning of 1990. Data from three nationwide computerized health care registers (Medication Reimbursement Register, Hospital Discharge Register and Pension Register) was used to identify from the Finnish population all persons born from 1940 to 1976 who had received a diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder ($n=33731$). After the patients had been identified, the National Population Register was used to link the patients to their first-degree relatives. The study protocol was accepted by the Ethics Committee of the National Public Health Institute and the Hospital District of Helsinki and Uusimaa, and the study was approved by the Ministry of Social Affairs and Health of Finland. Each affected subject was only contacted after having permission from the treating physician, and remaining family members contacted after the affected subject had given consent. All study subjects gave written informed consent for the study protocol.

From the identified families, two samples assumed to have a high genetic risk for schizophrenia were selected, one of which was a nationwide sample of randomly selected 643 families with at least two or more siblings with a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder and at least two siblings with no psychiatric diagnosis. This nationwide sample was used in the Studies of the current thesis.

From the aforementioned 643 families a subsample was randomly selected in order to collect more detailed phenotypic information. For this sample a

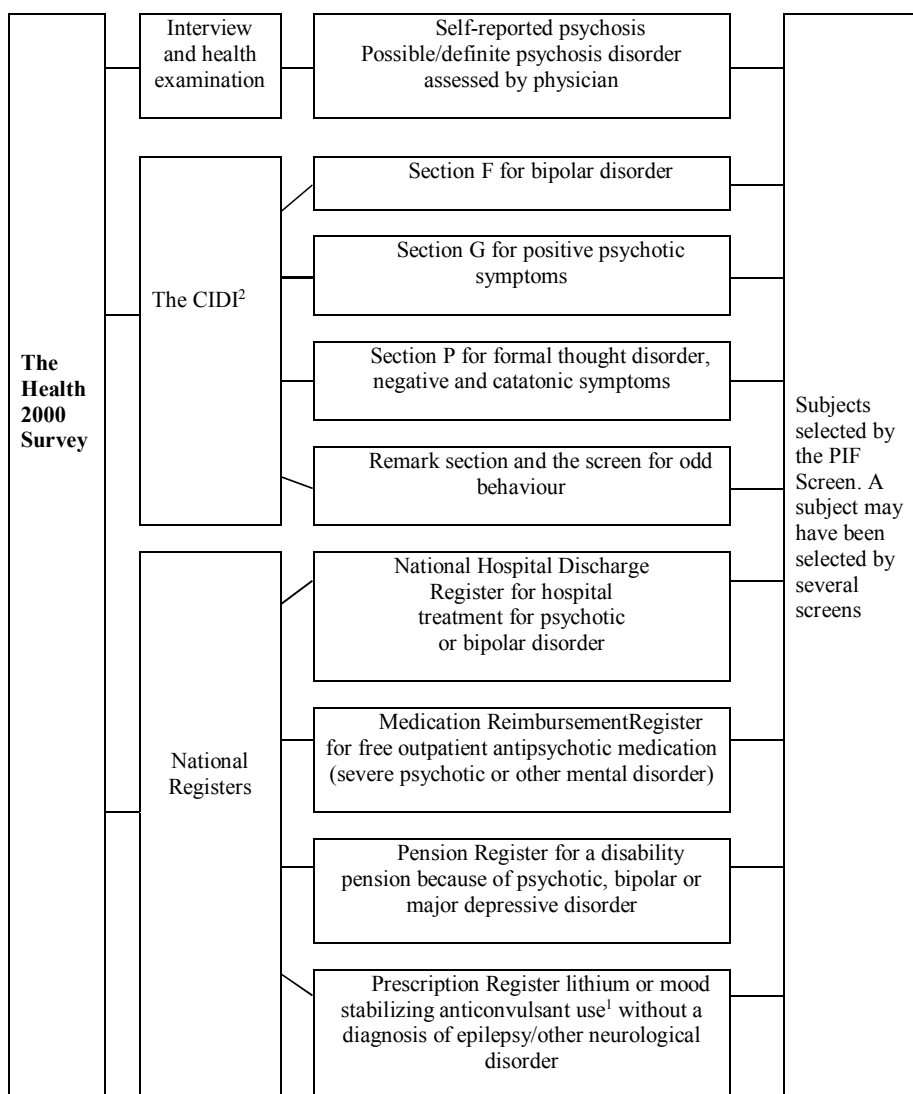
psychiatric interview using the Clinician Version of the SCID interview for DSM-IV (SCID-I for Axis I disorders and SCID-II for Axis II disorders, First et al., 1997), neuropsychological assessment and several rating scales were conducted. The interviewers were psychiatrists, psychologists or advanced psychiatric nurses who were trained and supervised in the use of these instruments. Case records were collected for hospital and outpatient treatment for mental disorders. The lifetime diagnosis for each patient was assessed by two psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 1994), independently of each other. The Operational Criteria Checklist for Psychotic Illness OPCRIT (McGuffin et al., 1991) was also filled by one of the assessors. In case of disagreement, the diagnosis was also assessed by a third psychiatrist, and a consensus diagnosis was established. All available medical records, the OPCRIT process and the SCID interview were used when assessing the final consensus diagnosis. Altogether, 305 subjects from 63 families were collected. All families in the sample represented familial schizophrenia. In each of the families there was at least one sibling with a diagnosis of schizophrenia, plus at least one other sibling with schizophrenia, schizoaffective disorder or schizophreniform disorder (Hoti et al., 2004).

3.1.2 The Health 2000 Survey and the Psychosis in Finland

The Health 2000 study is a Finnish general population health survey of a nationally representative two-stage cluster adult sample of 8028 persons aged thirty or over (<https://thl.fi/fi/tutkimus-ja-kehittaminen/tutkimukset-ja-hankkeet/terveys-2000-2011>). Additionally, a young adult cohort including 1894 subjects aged 18-29 years in the year 2000 was collected (Koskinen et al., 2005). The Health 2000 baseline study took place between September 2000 and June 2001. It consisted of a home interview and a health examination at the local health centre, or a condensed interview and health examination at home or institution for those unable to attend in the healthcare centre. A telephone interview or a mail questionnaire was arranged for remaining subjects. Register information was gathered for the whole sample in order to complement baseline information and for follow-up purposes. The Hospital District of Helsinki and Uusimaa approved of the study design, and written informed consent was obtained from the participants.

The health examination of the Health 2000 study included a shortened version of the Munich-Composite International Diagnostic Interview or M-CIDI (Wittchen et al. 1998). The interview included the sections on depression, mania, anxiety, psychotic symptoms and substance use. However, M-CIDI alone is not a reliable instrument for diagnosing psychotic disorders (Kendler et al. 1996). Hence, the Psychoses in Finland (PIF) study, a substudy of the Health 2000 focusing on epidemiology of psychotic disorders in Finland, was conducted. The whole baseline adult sample of the

Health 2000 survey was screened for possible psychotic disorders with a so-called PIF Screen (Perälä, 2007) consisting of several elements, outlined in Figure 1. Items from the M- CIDI interview that were utilized in the screen are presented in Table 4.



¹ Between 1996-2002

² the Munich Composite International Diagnostic Interview

Figure 1. The Psychoses in Finland (PIF) Screen

Table 4. TheM-CIDI¹ sections

Section F screen for bipolar disorder	Positive if a subject had had a lifetime episode of elevated or irritable mood lasting at least four days and had at least three out of twelve manic-like symptoms in the CIDI. The symptoms did not have to be concurrent with the elevated or irritable mood
Section G screen for positive psychotic symptoms with clinical relevance	Positive if a subject had experienced any of the 22 psychotic-like symptoms probed in the CIDI, if the symptom had had clinical relevance (had interfered with normal life or if the subject had talked about them to a healthcare professional), or a subject reported three or more symptoms regardless of clinical relevance
Section P screen for formal thought disorder, negative and catatonic symptoms	Positive if during the CIDI interview, as assessed by the interviewer there were symptoms of positive formal thought disorder, negative symptoms, behaviour suggesting the subject is having hallucinations or catatonic symptoms
Remark section and the screen for odd behaviour	The interviewer noted remarks concerning the individual and the interview. If a subject was not selected by any other screen, but these remarks were indicative of a psychotic disorder, the screen was positive

¹ the Munich Composite International Diagnostic Interview

If any of the screening elements were positive, the subject was invited for a re-interview (n=746). The re-interview consisted of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al. 1997), neuropsychological assessment and several rating scales. Hospital and outpatient case notes from psychiatric and primary care units from all lifetime treatment contacts for all mental health problems of the subjects were also collected, with the approval of the Finnish Ministry of Social Affairs and Health. Final diagnoses were based on a consensus between interviewer and clinical supervisor using data from the SCID-I interview and medical records from possible mental health treatment. The current study included a group of subjects who had psychotic- or manic-like experiences based on the CIDI, but who did not get a diagnosis of a psychotic disorder with the thorough diagnostic procedure during the PIF study (n=430).

A sample of subjects comprising the group of population controls was also randomly selected from participants of the Health 2000 study (n=174). Of the selected controls, 24 were selected by the PIF screen and not used as part of the control group for these analyses. These selected 150 controls were also invited for a re-interview, and 114 persons were assessed with psychiatric and neuropsychological methods also included in the family sample study described above.

3.1.3 The Health 2011 Survey

The Health 2011 Survey (<https://thl.fi/fi/tutkimus-ja-kehittaminen/tutkimukset-ja-hankkeet/terveys-2000-2011>) is a follow-up study of the Health 2000 Survey. All participants of the Health 2000 Survey who were alive and living in Finland and who had not refused further contact (Markkula et al. 2015; Koskinen, 2012) were included. The survey included a general health interview, during which sociodemographic information and psychiatric disorders diagnosed by a physician were asked for. Psychiatric disorders at follow-up were assessed with the M-CIDI (Wittchen et al. 1998) sections for depressive, anxiety and alcohol use disorders.

3.2 Study I

3.2.1 Family sample

From the 63 families with members with schizophrenia, schizoaffective or schizophreniform disorder who were thoroughly assessed, further exclusions were made in order to analyse neuropsychological performance between the groups of affected subjects, their healthy siblings and control subjects from the general population. From the patients with schizophrenia (n=105) and their healthy relatives with no lifetime mental disorder (n=106), all parents as well as siblings over 70 years of age were excluded (5 patients, 28 healthy relatives). Other exclusion criteria were lack of co-operation (due to symptoms of schizophrenia, 14 patients), current alcohol or substance use disorders (4 patients), and finally mental retardation or neurological disorder (1 patient). After exclusions, the final study sample included 81 schizophrenia patients and 78 healthy siblings from 58 families. Within the group of affected subjects, mean age of onset was 23.0 years, varying from 14 to 42 years. Almost all affected subjects were on antipsychotic medication, often with polypharmacy. No siblings had antipsychotic medication, but one reported benzodiazepine use.

3.2.2 Control group

From the aforementioned 114 control subjects from the Health 2000 study adult sample, we excluded subjects with a lifetime diagnosis of any psychotic disorder, current alcohol or substance use disorder, mental retardation or neurological disease, as well as subjects who were 70 years or older. In addition, subjects with a family history of mental disorder (assessed by self-report at interview) were excluded. After exclusions, 55 subjects fulfilled the inclusion criteria. At this point the mean age of the control sample was significantly higher than that of the family sample. Hence, we randomly selected 15 control subjects from the aforementioned Health 2000 young

adult cohort sample (Koskinen et al, 2005). These subjects were assessed with the same interview and neuropsychological methodology as the adult sample, and similar inclusion requirements were applied. The final population-based control group in Study I comprised 70 subjects.

3.3 Study II

3.3.1 Family sample

Subjects for Study II were from the same 63 families as in Study I, but for Study II all affected subjects with a schizophrenia spectrum psychotic disorder were included in order to have more statistical power. In this study we first excluded subjects who were over 70 years of age (21 relatives, 1 subject with schizophrenia), and those who were untestable for neuropsychological assessment due to lack of co-operation or interruption in the testing situation (3 relatives and 18 affected subjects). Further, all parents were excluded (10 relatives, 4 affected subjects). Other exclusion criteria were current alcohol or substance use disorders (6 affected subjects and 10 non-psychotic siblings), and mental retardation or neurological disorder (1 affected subject and 1 non-psychotic sibling). After the exclusions the final study sample comprised 91 siblings with a schizophrenia spectrum psychotic disorder (73 subjects with schizophrenia, 12 with schizoaffective disorder and 6 with schizophreniform disorder) and 105 unaffected siblings from 56 families. The affected subjects had a mean age of onset of 24.3 years (varying from 14 to 50 years, information available for 93% of the affected subjects). Almost all of the affected subjects were on antipsychotic medication, often with several psychotropic drugs.

For Study II the unaffected siblings were further divided into a group of 30 siblings with non-psychotic psychiatric disorders, and a group of 75 siblings without any psychiatric disorder. Among those with non-psychotic psychiatric disorders there were 12 persons with anxiety disorder, 7 with depressive disorder and 7 with a diagnosis of lifetime substance use disorder. Three subjects had comorbid depressive and anxiety disorder, and one person had comorbid depressive and eating disorder as well as dependent personality disorder. The study diagnoses were based on SCID interviews complemented by case notes when available. Of the siblings with non-psychotic psychiatric disorders, 3 reported using antidepressants, 2 using sedatives and one using both an antidepressant and a sedative.

3.3.2 Control group

The same control group as in Study I was used as a basis for the control group in Study II. For Study II the subjects who had not filled in the

Chapman anhedonia scales (which were used in the study) were excluded, hence the control group consisted of 67 subjects.

3.4 Studies III and IV

For Studies III and IV, psychotic-like or manic-like experiences reported in the CIDI during the PIF screening procedure described earlier were used as inclusion criteria (see Table 3 for more detail on the CIDI sections for PLEs and MLEs). Altogether 430 PIF subjects with a possible psychotic disorder had valid data from both the aforementioned SCID I interview and the CIDI.

For Studies III and IV the control group comprised only the Health 2000 study adult sample (the aforementioned 114 subjects from the Health 2000 adult sample before exclusions), because there were no significant differences between mean ages of study groups in Studies III and IV.

3.4.1 Baseline (Study III)

Exclusion criteria for baseline (Study III) are presented in Figure 2. Of note, people who in the CIDI interview reported that PLEs or MLEs had been due to alcohol/substance use were also meant to be excluded, but there were no such subjects left after other exclusions. After exclusions, the groups of subjects with PLEs (n=90) and MLEs (n=52) were formed. From the 114 control subjects with no psychotic symptoms in the PIF Screen and valid data from the CIDI as well as from neuropsychological assessment, there remained 66 subjects after exclusions. For controls, family history of psychotic disorders was asked for during the interview.

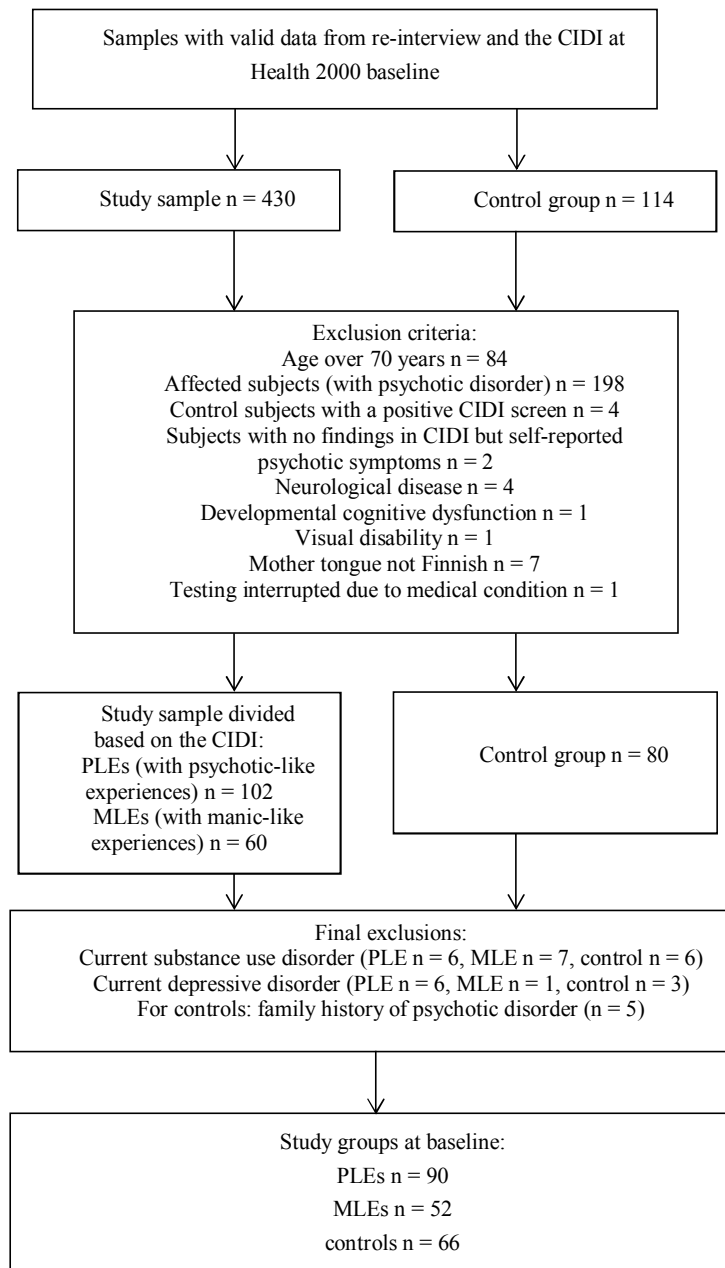


Figure 2. Exclusion criteria for baseline in Study III

3.4.2 Follow-up (Study IV)

Data for follow-up came from two sources. First, interview data was obtained for those baseline subjects who were alive and participating in the Health 2011 Survey. This included subjects with psychotic-like experiences (PLEs) at baseline (n=86), subjects with manic-like experiences (MLEs) at baseline (n=45) and control subjects (n=62).

Second, register data on hospitalizations for psychiatric disorders, dementia, suicide attempt or death during follow-up period (2000-2011) was obtained for all study subjects (subjects with PLEs n=90, subjects with MLEs n=52 and controls n=66). This information was also obtained for those subjects who had died during the follow-up or refused to participate. The information was gathered from the Care Register for Health Care (HILMO, former national hospital discharge register) managed by the National Institute for Health and Welfare. It covers all public and private hospitals in Finland for hospitalizations. Also, information of free outpatient antipsychotic medication, for severe psychotic or other severe mental disorders, from the Medical Reimbursement Register of the Finnish Social Insurance Institution was obtained for all of the baseline subjects.

3.5 Neuropsychological assessment

Neuropsychological assessment consisted of internationally used and validated tests. The selected test battery was presented to all study subjects in a fixed order. Examiners were extensively trained and supervised in the use of the tests. The tests were scored following standardized procedures. The following cognitive domains were assessed.

General ability was measured with the Vocabulary subtest of the Wechsler Adult Intelligence Test–Revised (WAIS-R) (Wechsler, 1981). The test reflects verbal concept formation. It is usually well preserved in different neurological conditions and is considered to be the best single measure of general ability and premorbid intellectual functioning (Lezak et al. 2004).

Visual-motor performance was measured with the Digit Symbol task of the WAIS-R. It is a task reflecting a multitude of performance efficiency functions such as processing speed, response-orientation and search for an appropriate code (Andrewes, 2016).

Simple auditory attention was measured with the Digit Span Forward subtest of the Wechsler Memory Scale–Revised (WMS-R) (Wechsler, 1987). Verbal working memory was assessed with the Digit Span Backward subtest of the WMS-R.

Simple visual attention was measured with the Visual Span Forward subtest and visual working memory with the Visual Span Backward subtest of the WMS-R.

Several variables from the California Verbal Learning Test (CVLT) (Delis et al, 1987) were used to measure verbal learning and memory. In the CVLT the examinee is required to learn a 16-item word list over five trials and to recall/recognize items on the list after a short and longer (approximately 20 minutes) delay. It yields several parameters that can be used as independent variables. The verbal memory variables included in all of studies (Studies I-IV) were:

- 1) Total recall from trials 1-5 as the variable for learning, which is the number of words recalled during all five trials.
- 2) The semantic clustering score for learning strategy. The score indicates the use of a learning strategy during learning task in order to reorganize words of the list into categorical groups.
- 3) The short delay recall was used as a measure for immediate recall of the material learned after five trials.
- 4) The long delay recall was used as a measure for delayed recall of the material learned after five trials.

In addition to these variables of the CVLT, in Study I the learning slope index was used to measure increase in recalled words per trial, and the recall errors indices (perseverative and intrusion errors) were used to measure repetition and intrusive errors during the task. In Study I, the cued versions of the short and long delay recall tasks were also used.

The efficiency of visual scanning, attention and mental flexibility were assessed with parts A and B of the Trail Making Test (TMT) (Reitan and Wolfson, 1993). Part A (TMT A) is a measure of simple visual-spatial attention and performance speed, whereas part B (TMT B) also requires executive functions (ability to shift attention and strategy) and visual working memory (Lezak et al, 2004). Performance time was used in the analyses, and possible errors made by the examinee were not corrected by the examiner. In Study I the difference score B-A, that diminishes the effect of the speed component and emphasizes the executive aspect of the task (Lezak et al, 2012), was also used.

Raw scores were used in all Studies and the performance of the study groups was compared to that of control subjects. Higher scores indicated better performance in all tests, except in the TMT and in the perseverative and intrusive errors of the CVLT.

3.6 Rating scales and questionnaires used

3.6.1 Schizophrenia family data

In Study II, anhedonia was measured with two of the Chapman Psychosis-Proneness scales, the Revised Social Anhedonia Scale (RSAS) (Mishlove et al, 1985) and Physical Anhedonia Scale (PAS) (Chapman et al, 1976). They are true/false questionnaires developed to measure individual differences in the capacity to experience pleasure from social/interpersonal and physical/sensual sources (Horan et al, 2006). The RSAS has 40 and the PAS 60 items and the sum of these two sets of items were used as the variables for social and physical anhedonia in Study II. The original English versions of the scales were translated into Finnish and back-translated blindly into English by a professional English translator, after which the original versions and the back-translated version were compared and corrections made accordingly (Miettunen et al, 2010).

3.6.2 Psychosis in Finland and control data

The Finnish versions of the following rating scales and questionnaires were used in the Health 2000 Study and hence available for Study III: Global Assessment of Functioning (GAF) (Ramirez et al. 2008) for current psychosocial functioning, Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al. 1992) for current social and occupational functioning and Beck Depression Inventory (BDI) (Beck et al. 1961) for current depressive symptoms. The GAF was evaluated as a part of the interview, as instructed in the DSM-IV (APA, 2000). In the Health 2011 follow-up survey there were some changes in the measures used (due to economic and time constraints). Hence the General Health Questionnaire (GHQ-12) was used for screening current psychological distress (Goldberg, 1972) and the thirteen-item version of the Beck Depression Inventory (BDI-13; Beck and Beck, 1972) for current depressive symptoms. The 13-item version has been shown to perform equally well previously (Aalto et al. 2012).

3.7 Statistical methods

3.7.1 Statistical methods for Study I

A generalized estimating equation (GEE) model that estimates population-averaged regression coefficients (Zeger, 1986) was used for comparison of neuropsychological test performance between groups of schizophrenia patients, healthy siblings and controls. This model was used to control for family correlation as the data was derived from families and thus could not be considered independent. Statistical models were adjusted for age, gender and education, since all of them may have had a modifying effect on cognitive

functioning (Lezak et al, 2004). The analyses were carried out with the Stata statistical software, version 8.2 (StataCorp, 2003). The type I error was controlled for by Bonferroni correction and $p < .002$ was considered significant, while $p < .05$ but $> .002$ were considered indicative of significance. Effect sizes (d) were also calculated (Cohen, 1988).

3.7.2 Statistical methods for Study II

The internal consistency of responses for social and physical anhedonia was calculated with Cronbach α . Comparison of anhedonia scores between groups of subjects with schizophrenia spectrum disorders, unaffected siblings with non-psychotic disorders, unaffected siblings without non-psychotic disorders and controls were carried out with a similar GEE model that estimated population-averaged regression coefficients (Zeger, 1986) in Study I, in order to control for the family correlation. All models were also adjusted for gender, since gender differences in reported anhedonia levels are common (Erlenmeyer-Kimling et al, 1993; Miettunen et al, 2010). These statistical analyses were carried out using the Stata statistical software, version 9.0 (StataCorp, 2005).

Random effects model was used to investigate independent effects of social and physical anhedonia, group membership (schizophrenia spectrum disorders, unaffected siblings and controls), age, education and gender on neuropsychological variables. In these analyses, family membership was used as a random effect to control for the within-family correlation. The Wald test was used to calculate group status x social/physical anhedonia interactions on neuropsychological variables.

Differences in neuropsychological performance between unaffected siblings with and without non-psychotic disorders, as well as between the siblings with non-psychotic disorders and controls were also analysed with a similar GEE model as in comparisons of anhedonia scores. These analyses were adjusted for age, gender and education, since all of them have a modifying effect on cognitive function (Lezak et al, 2004). Finally, a random effects model described above was used to investigate the effects social and physical anhedonia, group membership, age, education and gender on neuropsychological variables with both social and physical anhedonia as predictors in the same model. Also, in Study II the type I error was controlled for with the Bonferroni correction and p values $< .004$ were considered significant.

3.7.3 Statistical methods for Study III

SPSS software version 21.0 was used in the analyses for Study III. Pearson's Chi-Square test was used to compare differences between groups in gender, education level (as a categorical variable basic, secondary or high) and lifetime non-psychotic psychiatric diagnoses (yes or no). Differences in

continuous variables (age, GAF, SOFAS and BDI scores) between the study groups were explored with one-way analysis of variance (ANOVA).

The differences in neuropsychological performance between the study and control groups were analysed with linear regression modelling. These were conducted separately between each study group and the control group and also between all of the study groups. Age and gender were used as covariates. As education level did not differ between groups, it was not included in these between-group analyses.

3.7.4 Statistical methods for Study IV

SPSS software version 23 (IBM Statistical Software, IBM Corp.) was used for the analyses. Differences between groups of subjects with PLEs, MLEs and controls in gender, self-reported health status (good or rather good on a Likert scale), family status and employment status were calculated with the Pearson's Chi-Square Test. One-way ANOVA was used to calculate differences in age, BDI-13 and GHQ-12 scores. For analysis on baseline variables predicting psychiatric condition at follow-up a binary logistic regression model was used. For these analyses a variable "any psychiatric disorder during follow-up" that combined information from HILMO register, interview data and the CIDI was formed. This was done in order to have more statistical power in analyses. In the case of a subject having information of psychiatric disorders from several sources, register information was considered first, then information from interview and the CIDI so that each subject was represented as one case with/without diagnosis.

4 RESULTS

4.1 Cognitive performance of schizophrenia patients, healthy siblings and population controls (Study I)

Demographic characteristics of the study groups and mean and standard deviations of cognitive variables within each group and between-group comparisons are presented in Tables 5 and 6. The groups differed regarding age and education: the affected subjects were slightly younger and had a lower education level than the other groups (with p values .01 and .0001, respectively).

Table 5. Mean and standard deviations of demographic characteristics in subjects with schizophrenia, healthy siblings and population controls

	Subjects with schizophrenia n = 81		Healthy siblings n = 78		Control subjects n = 70		p
M/F distribution	42 / 39		39 / 39		35 / 35		.95 ^a
	Mean	SD	Mean	SD	Mean	SD	
Age	44.5	7.3	48.8	9.5	46.6	13.0	.01 ^b
Education (years)	10.1	1.8	11.1	2.5	12.7	3.5	.0001 ^b

^aChi²

^bOne-way ANOVA

Table 6. Mean and standard deviations of neuropsychological variables and comparison between groups of subjects with schizophrenia, healthy siblings and controls in Study I^a

	Subjects with schizophrenia n = 81		Healthy siblings n = 78		Control subjects n = 70		1. Affected vs. siblings	2. Affected vs. controls	3. Siblings vs. controls
	Mean	SD	Mean	SD	Mean	SD	<i>p</i>	<i>p</i>	<i>p</i>
Vocabulary ¹	28.1	13.3	40.8	11	41.9	10.4	<.0001	<.0001	.18
Digit span forward ²	5.9	1.9	6.9	1.9	7.7	1.9	<.0001	<.0001	.12
Digit span backward ²	4.6	1.7	5.9	2.3	6.4	1.9	<.0001	<.0001	.54
Visual span forward ²	7.3	1.8	9.0	2.0	8.5	2.0	<.0001	<.0001	.13
Visual span backward ²	6.2	2.4	8.2	1.8	8.2	1.8	<.0001	<.0001	.83
Total recall ³	31.9	12.0	45.0	10.6	49.7	9.8	<.0001	<.0001	.06
Learning slope ³	0.8	0.5	1.14	0.56	1.4	0.6	<.0001	<.0001	.07
Semantic categories ³	6.2	4.9	11.6	6.8	15.7	9.0	<.0001	<.0001	.02
Intrusions ³	7.2	13.4	4.9	5.7	2.4	3.4	.79	<.0001	.01
Perseverations ³	3.9	6.1	6.5	2.7	4.3	4.5	.15	.78	.10
Immediate recall, free ³	6.7	3.3	9.4	2.7	10.7	3.1	<.0001	<.0001	.05
Immediate recall, cued ³	8.0	2.9	10.5	2.6	11.7	2.6	<.0001	<.0001	.03
Delayed recall, free ³	7.2	3.4	10.2	2.6	11.3	3.2	<.0001	<.0001	.13
Delayed recall, cued ³	7.8	3.4	10.6	2.5	11.8	2.8	<.0001	<.0001	.12
Trail Making Test A	67.8	31.4	44.5	24.6	32.2	13.2	<.0001	<.0001	<.0001
Trail Making Test B	166.6	84.7	119.7	64.0	83.0	40.7	<.0001	<.0001	<.0001
Trail Making Test B-A	102.3	66.4	77.7	54.5	50.8	36.7	.014	<.0001	.001
WAIS-R Digit symbol ¹	28.9	10.6	43.1	13.9	52.8	15.0	<.0001	<.0001	<.0001

¹ the WAIS-R² the WMS-R³ the CVLT^a models adjusted by age, education and gender

The main differences between healthy siblings and control subjects were found in neuropsychological tasks requiring performance speed and executive functions (Table 6). Siblings were significantly slower both in visual-motor and performance speed (measured with the Digit Symbol subtest of the WAIS-R, $p < .0001$, and the TMT A, $p < .0001$) than controls. Also, in tasks with an executive component (the TMT B and TMT B-A) the

siblings were slower than controls, with p values $<.0001$ and $.001$, respectively.

With the Bonferroni correction used in Study I, there were no more significant differences between siblings and controls. In these comparisons the effect sizes calculated were from small to moderate. The highest of those ($d=0.58-0.68$) were for measures of performance speed and executive functions (TMT A, B and B-A as well as the Digit Symbol test), and also with d varying between $0.51-0.59$ for some of the verbal memory measures used (using semantic categories as a learning strategy and making intrusive or perseverative errors during recall).

When comparing the affected subjects with schizophrenia and control subjects, the performance of the former group was significantly poorer in all neuropsychological measures used. In comparisons between the affected subjects and healthy siblings, the affected subjects still had poorer performance in almost all neuropsychological measures used, with an exception in the amount of perseverative or intrusive recall errors. The effect sizes calculated were mostly from moderate to large indicating a manifest cognitive dysfunction in the patient group.

4.2 Anhedonia and cognition in subjects with schizophrenia spectrum disorders, non-psychotic siblings and population controls (Study II)

Subjects with schizophrenia spectrum psychotic disorders had significantly higher levels of social and physical anhedonia than the siblings with or without non-psychotic psychiatric disorders or controls (with p values $.001$, $<.0001$ and $<.0001$, respectively). There were no differences in levels of social or physical anhedonia between groups of siblings with or without non-psychotic psychiatric disorders and controls. Cognitive performance of siblings with and without non-psychotic psychiatric disorders did not differ.

In separate random effects models for predictors of performance on each neuropsychological variable, physical or social anhedonia, age, gender, education and the effect of having a schizophrenia spectrum disorder or having familial vulnerability (siblings from families with schizophrenia) were included as predictors. Family membership was used as a random effect to control for the within-family correlation. In the first model with physical anhedonia, higher physical anhedonia associated with poorer performance in several variables of the CVLT used to measure verbal learning and memory. Coefficients for the effect of increase in scores of physical anhedonia were: effect coefficient $=-0.28$, $p=.001$ for CVLT total recall, effect coefficient $=-0.16$, $p=.003$ for semantic clustering and effect coefficient $=-0.06$, $p=.004$ for

delayed recall. Additionally, higher physical anhedonia associated with lower performance in concept formation as measured with the WAIS-R Vocabulary subtest (effect coefficient=-0.30, $p=.0001$). Having a schizophrenia spectrum disorder associated significantly with poor performance in all cognitive domains assessed here. Being a sibling from a family with schizophrenia associated with slower performance in the Digit Symbol subtest of the WAIS-R (effect coefficient=-5.48, $p=.001$) but not with other cognitive variables. In a second model with social anhedonia as one of the predictors, social anhedonia was not associated with performance in any of the neuropsychological measures. In this model with social anhedonia, having a schizophrenia spectrum disorder was significantly associated with poor performance in all neuropsychological domains explored in this study. Being a sibling from a family with schizophrenia associated with slower performance in the Digit Symbol test (effect coefficient=-5.58, $p=.001$).

4.3 Psychosocial and cognitive characteristics of subjects with psychotic-like or manic-like experiences (Study III)

There were differences in sociodemographic and clinical characteristics between the PLE group, the MLE group and controls. Subjects with MLEs were less often married or cohabiting, had more lifetime non-psychotic psychiatric diagnoses as well as more psychiatric comorbidity than controls or subjects with PLEs. The characteristics of the study groups are presented in Table 7.

Table 7. Demographic characteristics of controls, subjects with psychotic-like experiences and subjects with manic-like experiences

	Controls n = 66		Subjects with psychotic-like experiences n = 90		Subjects with manic-like experiences n = 52		<i>p</i>
	Mean	SD	Mean	SD	Mean	SD	
Age	50.6	10.1	49.5	10.3	46.8	9.5	.12 ^a
Gender (M/F)	32/34		35/58		24/28		.22 ^b
Education level¹	%		%		%		
Basic	32		23		25		
Secondary	36		33		33		
High	32		39		33		
Current employment¹							
Full/part-time	63.5		72		79		
Married/cohabiting	79		78		56		.007 ^b
Lifetime non-psychotic disorders	39		34		62		.003 ^{b,2}

^a One-way ANOVA, $p < .05$ was considered significant

^b Chi², $p < .05$ was considered significant

¹ Education level was classified as basic (comprehensive school or equal), secondary (occupational school/upper secondary school) and high (university degree or similar), classification designed for the T2000 Health Survey (Aromaa & Koskinen, 2004)

² In additional analyses, the subjects with MLEs had significantly more lifetime non-psychotic diagnoses than the controls ($p = .01$) or the subjects with PLEs ($p = .001$)

In general, differences between groups in neuropsychological variables, the BDI, the GAF and the SOFAS scores, were small (see Table 8). The subjects with MLEs had significantly higher scores in the BDI ($p=.04$), and significantly lower scores in the GAF ($p=.02$) than the controls. The subjects with PLEs only had significantly lower scores than controls in the GAF ($p=.02$). The subjects with PLEs were slightly, but significantly, slower than controls in the TMT A ($\beta=0.149$, $p=.04$), and subjects with MLEs slightly slower than controls in the Digit Symbol subtest of the WAIS-R ($\beta=-0.146$, $p=.04$), but no other significant differences in cognitive performance were found.

Table 8. Mean and standard deviations and between-group comparisons of neuropsychological variables, the BDI, the GAF and the SOFAS scores in Study III

		Controls n = 60	Subjects with psychotic- like experiences n = 90	Subjects with manic- like experiences n = 52	Controls vs. subjects with PLEs	Controls vs. subjects with MLEs	Subjects with PLEs vs. subjects with MLEs
		Mean (SD)	Mean (SD)	Mean (SD)	<i>p</i>	<i>p</i>	<i>p</i>
Vocabulary ¹		42.1 (10.3)	42.1 (10.8)	40.2 (10.7)	.94	.17	.16
Digit span	forward ²	7.3 (1.8)	7.4 (2.3)	7.2 (2.2)	.85	.33	.34
Digit span	backward ²	6.0 (1.7)	6.0 (1.7)	6.0 (1.6)	.90	.48	.33
Visual span	forward ²	7.9 (1.7)	8.2 (1.8)	8.4 (2.1)	.51	.88	.99
Visual span	backward ²	7.8 (1.8)	8.0 (2.1)	8.1 (1.8)	.85	.97	.89
Total recall ³		47.8 (10.8)	51.1 (10.1)	51.8 (11.9)	.09	.25	.89
Semantic categories ³		15.2 (9.8)	17.6 (10.2)	18.5 (13.2)	.14	.37	.75
Immediate recall ³		10.4 (3.5)	11.2 (2.8)	11.2 (3.1)	.17	.75	.49
Delayed recall ³		10.7 (3.6)	11.7 (2.8)	11.7 (3.2)	.06	.51	.46
TMT A		33.3 (12.9)	36.6 (17.1)	33.6 (10.5)	.04	.12	.93
TMT B		88.5 (43.8)	91.3 (48.2)	83.2 (32.3)	.21	.54	.69
Digit Symbol ¹		50.0 (14.8)	50.3 (14.3)	50.3 (13.9)	.28	.04	.20
BDI		4.8 (5.0)	6.0 (4.4)	7.3 (8.1)	.12	.04	.23
SOFAS		83.3 (9.2)	80.4 (10.9)	81.0 (8.5)	.08	.17	.75
GAF		82.9 (9.4)	79.0 (10.8)	78.8 (9.2)	.02	.02	.90

Abbreviations: TMT, the Trail Making Test, BDI, The Beck Depression Inventory, SOFAS, the Social and Occupational Functioning Assessment Scale, GAF, the General Assessment of Functioning

¹ WAIS-R

² WMS-R

³ CVLT

^a linear regression analyses with age and gender as covariates, $p < .05$ was considered significant

^b One-way ANOVA, $p < .05$ was considered significant

4.4 Associations of psychotic-like or manic-like experiences with later psychiatric disorders: an 11-year follow-up (Study IV)

Characteristics of the study groups at follow-up are presented in Table 9. There were more deaths during the follow-up period in the MLE group (11.5%) than in other groups (PLE group 3.3% and controls 4.5%) but otherwise loss to follow-up of study subjects was fairly low. Groups did not differ significantly in self-reported health status, marital or employment status at follow-up. The severity of reported depressive symptoms as measured with the BDI-13 or current psychosocial distress measured with the GHQ-12 did not differ significantly between the groups.

Table 9. Characteristics of the controls, subjects with psychotic-like experiences and subjects with manic-like experiences at 11-year follow-up

	Controls n = 62	Subject with psychotic-like experiences (PLEs) n = 86	Subjects with manic-like experiences (MLEs) n = 45	<i>p</i>
Gender (M/F)	30/32	32/54	20/25	.38 ^b
Age	58.8 (9.8) ¹	57.2 (9.8) ¹	54.5 (9.1) ¹	.08 ^a
BDI-13	3.2 (4.7) ¹	3.7 (3.7) ¹	3.9 (4.2) ¹	.71 ^a
GHQ-12	2.0 (3.3) ¹	2.2 (3.2) ¹	2.1 (2.6) ¹	.95 ^a
	%	%	%	
Good/nearly good health status at 2011	66.1	67.4	53.3	.51 ^b
Married/ cohabiting	79.0	76.8	66.7	.31 ^b
Full/ part-time employment	48.9	48.9	51.5	.66 ^b

Abbreviations: BDI, the Beck Depression Inventory; GHQ, the General Health Questionnaire

^a One-way ANOVA

^b Chi²

¹ Mean, SD

The prevalence of mental disorders at follow-up in each group is presented in Table 10. The subjects with MLEs had the highest prevalence of psychiatric disorders with a significant difference to the controls and the subjects with PLEs. Subjects with PLEs and controls did not differ in prevalence of psychiatric disorders during follow-up. Comparisons were first calculated only for a condition of any psychiatric disorder at follow-up due to small numbers in specific diagnostic categories. However, in additional analysis, there were no significant between-group differences in the amount of any

depressive disorder during follow-up (with p values of p .85 for controls vs. PLEs, p .29 for controls vs. MLEs and p .34 for PLEs vs. MLEs). In these analyses, subjects with comorbid depressive and anxiety disorder were included.

There was only one subject, with baseline MLEs, who developed a psychotic disorder during follow-up. There was no elevated amount of dementia diagnoses in groups with PLEs or MLEs in the follow-up.

Table 10. Psychiatric diagnosis at 11-year follow-up in controls, subjects with psychotic-like experiences and in subjects with manic-like experiences

	Control s n = 66		Subjects with psychotic- like experiences (PLEs) n = 90		Subjects with manic- like experiences (MLEs) n = 52		Cont rols vs. PLEs	Cont rols vs. MLEs	PL Es vs. MLEs
	n	%	n	%	n	%	p^a	p^a	p^a
Schizophrenia	-	-	-	-	1	1.9			
Bipolar disorder	-	-	-	-	-	-			
Depressive disorder	6	9.1	7	7.8	8	15.4			
Anxiety disorder	1	1.5	2	2.2	2	3.8			
Comorbid depressive and anxiety disorder	-	-	2	2.2	1	1.9			
Alcohol use related disorder	2	3.0	3	3.3	3	5.8			
Other psychiatric disorder	-	-	-	-	1	1.9			
Any psychiatric disorder^{1,2}	9	13.6	14	15.5	16	30.8	.74	.02*	.03*
Dementia	-	-	1	1.1	-	-			

¹ includes information from national registers as well as from interview and/or the Composite International Diagnostic Interview at follow-up

² diagnostic categories here include ICD-10 diagnoses for each diagnostic entity collected from the interview data. Register information also covered diagnoses for suicide attempt and death by suicide but these were not found among the study subjects

^a Chi². *significant $p < .05$

In logistic regression analysis on baseline variables associating with later psychiatric outcome with age, gender, PLEs or MLEs at baseline as predictors, MLEs at baseline associated with an increased risk for a future

psychiatric condition (OR 2.78, CI 1.1-7.02, p .03). However, when lifetime non-psychotic disorders at baseline were included in the model, previous association was no longer significant, with only lifetime psychiatric illnesses remaining highly significant predictors for future psychiatric disorders (OR 4.27, CI 1.94-9.36, $p < .0001$).

Cognitive performance at baseline was not significantly associated with later psychiatric disorders in any of the groups.

5 DISCUSSION

The aim of the present thesis was to explore two middle-aged populations who presumably had a higher risk for psychosis than the general population. From schizophrenia family participants, cognitive performance of siblings without current non-psychotic or psychotic psychiatric disorders was compared to that of population controls. Levels of social and physical anhedonia were studied in groups of siblings with and without non-psychotic disorders, patients with schizophrenia spectrum disorders and population controls. Associations of social and physical anhedonia with cognitive performance were also explored. From a general population survey, groups of participants with psychotic- or manic-like experiences, but with no diagnosable psychotic disorder, were formed. Cognitive performance and psychosocial functioning in these groups were compared to that of population controls. Additionally, the predictive value of psychotic- or manic-like experiences reported at baseline for psychiatric disorders at 11-year follow-up was explored.

5.1 Cognitive performance of affected subjects, healthy siblings and population controls (Study I)

In Study I, the main focus was to compare cognitive performance of healthy siblings of schizophrenia patients to that of representative population-based controls. The main finding was that healthy siblings had deficits in tasks that required performance speed and in tasks with an executive component. The siblings scored poorer than population controls both in the TMT A, requiring simple visual-motor and attention, and in the TMT B, which also requires set-shifting, divided attention and visual working memory. The results were in line with a meta-analysis on methodologically well-organized studies on relatives of schizophrenia patients (Snitz et al. 2006), in which medium effect sizes were found for performance differences in TMT A and B between relatives and controls.

Since the aforementioned tasks, used in Study I, had a performance speed component, it might be that these differences relate mostly to the slight slowness of performance of siblings in general. However, the difference between groups remained after the speed component was subtracted, suggesting that performance speed alone does not explain the difference and an executive component may also be involved. Subtle executive dysfunction in siblings of schizophrenia patients (milder than found in patients with

schizophrenia) has also been observed in previous meta-analyses (Snitz et al. 2006; Sitskoorn et al. 2004; Szoke et al. 2005). The TMT tasks have been found to associate with frontally mediated cognitive operations (Stuss et al. 2001), but it should be noted that since these tasks require coordination of a broad spectrum of cognitive abilities they are sensitive to brain dysfunction with different aetiologies, as well as to brain dysfunction with several areas of the brain (Andrewes, 2016).

Healthy siblings were slower in the Digit Symbol task than controls. Coding tasks requiring processing speed have systematically been found to be impaired in schizophrenia (Dickinson et al. 2007; Glahn et al. 2006). Digit symbol is also a task requiring several performance components and can be compromised regardless of the location of lesion (Lezak et al. 2004). Since coding tasks require rapid and smooth coordination of a complex assembly of elementary operations, poor performance in these tasks may implicate deficient coordination, or failures of effective connectivity among distributed brain networks, more than specific subprocesses (Dickinson et al. 2007).

Measures for performance speed and executive function used in Study I also have a visual-spatial component (visual scanning and searching for a target). In general, spatial tasks are complex and require a multitude of functions which means that deficits in those tasks may relate to several possible subprocesses (Andrewes, 2016). However, in a twin study of healthy and schizophrenic co-twins using a spatial delayed response task, the encoding or maintenance of spatial information was found to be the main deficit (Glahn et al. 2003). Considering this, it may be that spatial processing deficits contributed in part to the performance of siblings in TMT tasks and Digit Symbol task.

Verbal learning and memory measures did not differ statistically significantly between healthy siblings and population controls, although there were findings indicative of less efficient use of semantic categories and more recall errors in the CVLT in the siblings' group. Also previously, memory deficits in relatives of patients with schizophrenia have been mild and not always statistically significant (Cirillo and Seidman, 2003; Conklin et al. 2005). Most likely differences among studies also relate to the sensitivity of the methods used. The CVLT used in Study I has been found to be a less sensitive measure for verbal learning than some other methods, such as story recall (e.g. the Logical Memory task of the WMS-R) or other list learning tasks (e.g. Rey Auditory Verbal Learning Test) (Trandafir et al. 2006). This has been attributed to the relative ease with which presented words can be clustered based on their semantic features in the CVLT (Stone et al. 2011).

Verbal working memory as measured with digit span tasks did not differ significantly between healthy siblings and population controls. Previously, mild verbal working memory deficits have been found in healthy relatives of schizophrenia patients (Snitz et al. 2006; Trandafir et al. 2006), and the

deficits were found to scale in severity with genetic loading for schizophrenia (Tuulio-Henriksson et al. 2002). It has been suggested that relatives perform more poorly in working memory tasks with more executive demands (Conklin et al. 2005). The digit span tasks used in the current study are considered to be rather easy when compared with, for example, letter-number sequencing or n-back tasks (Horan et al. 2008b; Lezak et al. 2012). Neither general ability impairment nor severe memory dysfunction were found in siblings.

Schizophrenia patients were impaired in all areas of cognitive functioning compared with population controls and their healthy siblings. Findings are in line with previous studies on generalized cognitive impairment in schizophrenia (Heinrichs and Zakzanis, 1998; McIntosh et al. 2005; Franke et al. 2016).

5.2 Associations of anhedonia and cognition (Study II)

The aim of Study II was to compare levels of social and physical anhedonia among unaffected siblings and subjects with schizophrenia spectrum disorders and with a population-based control group, and to further explore associations of physical and social anhedonia with cognitive performance. In comparisons of levels of social and physical anhedonia, measured with the Chapman scales, the group of unaffected siblings was divided into those with and those without non-psychotic psychiatric disorders. Interestingly, there were no differences in the levels of physical or social anhedonia between groups of siblings with and without non-psychotic psychiatric disorders and population controls. Even though the study groups were small, this may suggest that, regardless of familial liability to schizophrenia or the presence of a non-psychotic psychiatric disorder, the siblings of affected persons do not necessarily have elevated anhedonia.

Elevated anhedonia in relatives of schizophrenia patients has previously been found in some (Kendler et al. 1996; Laurent et al. 2000), but not all studies (Craver and Pogue-Geile, 1999; Erlenmeyer-Kimling et al. 1993b). Inconsistent findings may at least partly relate to methodological differences as well as differences in study samples (Schürhoff et al. 2003). At biological level, deficits in subcortical dopamine signalling have been found to contribute to negative symptom severity and self-reported anhedonia independent of diagnostic status in healthy controls, siblings of schizophrenia patients and patients themselves (Eisenstein et al. 2017). Specifically, higher striatal D2-receptor binding was associated with less physical and social anhedonia across study groups (Eisenstein et al. 2017).

Subjects with schizophrenia spectrum disorder had significantly higher levels of both social and physical anhedonia than either their unaffected

siblings or population controls. Anhedonia is one of the negative symptoms of schizophrenia and has repeatedly been shown to be elevated in subjects with schizophrenia (Herbener et al. 2005; Horan et al. 2007). However, studies using different methodology for measuring anhedonia have yielded different results. While patients with schizophrenia reported more anhedonia in relation to anticipatory items (Gard et al. 2007), they have been found to report normal levels of pleasant emotions in laboratory studies focusing on state emotions (Cohen and Minor, 2010).

In analyses on associations of physical and social anhedonia with cognitive performance of the whole study population, elevated physical anhedonia was associated with verbal memory deficits and with lower verbal ability. There was no interaction of physical anhedonia and group status (schizophrenia spectrum disorder, non-psychotic sibling or control) indicating that the effect of physical anhedonia was similar in the general population subjects and subjects with a familial vulnerability to psychosis. There is a possibility that associations between physical anhedonia and verbal memory and verbal ability could at least partly be explained by the demands of the assessment method used (the Chapman Scales). Judgements concerning remembered or anticipated events and the pleasure associated with them require the subject to invoke an internal representation of the experience described in the questionnaire and make a judgement about the affective value of said representation (Gold et al. 2008). Being able to make those judgements requires cognitive processes including memory, insight, generalization and prediction that are often compromised in schizophrenia (Horan et al. 2006a; Rector et al. 2005) .

Social anhedonia did not associate statistically significantly with any of the cognitive variables measured. However, there were two associations suggestive of significance with verbal ability and verbal learning. Since there was no interaction between group status and social anhedonia it would seem that, as with physical anhedonia, the effect of social anhedonia on cognition was similar in all study groups. In the model including both physical and social anhedonia, only the effects of physical anhedonia on cognition remained significant, suggesting that elevated physical anhedonia may be more strongly related to cognition than social anhedonia. It should be noted though, that in Study II there were no measures of social cognition in our test battery. Previously, higher anhedonia has been found to correlate with worse performance on a measure of emotion perception which has an important role in social cognition (Herbener et al. 2008). Since impairment in social interaction is a common symptom in schizophrenia spectrum disorders (Velthorst et al. 2012), future studies addressing the relation of social anhedonia and impaired processing of emotional stimuli in subjects with vulnerability to schizophrenia are needed.

Anhedonia is considered to be one of the main features in negative symptom dimensions of schizophrenia (Wolf, 2006) as well as of negative schizotypy, which is considered to be a latent liability to schizophrenia on the level of personality with positive and negative schizophrenia-resembling symptoms (Lahti et al. 2009). Negative symptoms have been found to associate with a variety of cognitive domains in patients with schizophrenia (Lincoln et al. 2016; Szendi et al. 2006; Winograd-Gurvich et al. 2006). The relationship of cognitive deficits and negative schizotypal traits in subjects who have a genetic risk for developing schizophrenia is more complex (Delawalla et al. 2006). Our results in Study II suggest that elevated physical anhedonia relates to poorer performance in some of the verbal measures but separately from the effect of familial liability. In a meta-analysis by Snitz et al. (2006), schizotypal personality disorder or schizotypal symptoms did not have an effect on cognitive functioning of non-affected first-degree relatives of schizophrenia patients. A clinical high-risk study on adolescents suggested that the effects of genetic risk and clinical status on cognitive functioning are independent, and that cognitive impairment can occur in genetically vulnerable individuals regardless of their clinical status (Myles-Worsley et al. 2007).

However, social and physical anhedonia are only one dimension of negative symptoms. Since there are several different scales that are used to measure negative symptoms to begin with (Lincoln et al. 2017), our results should be interpreted within the context of self-reported ability, or the lack of it, in experienced physical and social anhedonia as measured with the Chapman scales. With new information on neural bases of experiences of emotion, it has been suggested that in the future studies on affective symptoms of schizophrenia need to be done with systematic methodology and be multidisciplinary, with enough emphasis on neural and cognitive processes behind reported experience of emotions (Cohen et al. 2011; Dollfus and Lyne, 2016).

5.3 Psychosocial and cognitive characteristics of subjects with psychotic-like or manic-like experiences (Study III)

Study III aimed at comparing cognitive performance and psychosocial functioning in subjects with psychotic-like or manic-like experiences (PLEs or MLEs) and controls from a general population survey sample of adults aged 30–70 years. No major differences in cognitive performance were found. Subjects with MLEs had slightly worse psychosocial functioning and more depressive symptoms than controls, although differences were small. They had also had more lifetime non-psychotic psychiatric disorders and more psychiatric comorbidity than controls. MLEs were also related to

interpersonal functioning, as subjects in this group were more often living alone than controls or subjects with PLEs. Altogether, these findings suggest more pronounced difficulties in daily life and also possibly in interpersonal relationships for people with MLEs than in the other groups, even though occupational functioning was at the same level as controls.

In patients with bipolar disorder, cognitive and emotional abnormalities, as well as impairment in subjective (i.e. perceived quality of life) and objective (i.e. occupational, physical and interpersonal) functioning, are often present (Martinez-Aran et al. 2007). It has been shown that cognitive deficits in these patients predict psychosocial outcome independently of mood symptoms (Van Rheenen and Rossell, 2014). Therefore, it is of interest that in Study III the subjects with MLEs who had a comparable cognitive ability to that of controls still had several similarities, albeit in a rather mild form, to bipolar patients in psychosocial and mood measures. This may suggest that when MLEs are present, they may have an influence on a person's life despite average occupational and cognitive functioning.

However, it has been suggested that mean age of onset for bipolar disorder may fall into three categories: having peaks in twenties, thirties and also forties with 55 % of patients in middle or late onset groups (Hamshere et al. 2009; Bauer et al. 2014). Hence, it is possible that there may have been subjects in our group with MLEs who are still at risk for later conversion to a bipolar disorder or another psychiatric condition.

The only significant difference between subjects with PLEs and controls was slightly worse psychosocial functioning. Interestingly, no differences in the amount of non-psychotic psychiatric disorders were found in subjects with PLEs and controls. The prevalence of PLEs has been found to be more than twice higher in individuals with depressive and anxiety disorders than in people without these disorders (Wigman et al. 2012). The results suggest that when studying subjects from the general population without a clinical framework, the presence of non-psychotic psychiatric conditions may be similar in subjects with and without PLEs. The results also differ from those found in the Adult Psychiatric Morbidity Survey (Freeman et al. 2011), but since we excluded subjects with a current psychiatric disorder our results are informative of the significance of PLEs when they are not part of a current psychiatric symptomatology.

5.4 Associations of psychotic-like and manic-like experiences with later psychiatric disorders (Study IV)

The aim of Study IV was to study whether PLEs, MLEs or neuropsychological performance at baseline associated with psychiatric disorders after an 11-year follow-up period. The main finding was that neither PLEs nor MLEs measured at the Health 2000 baseline assessment predicted conversion to psychosis during an eleven-year follow-up. In general, developing a psychosis during a follow-up is very rare. There was only one conversion to schizophrenia concerning a subject with baseline MLEs. During the follow-up, subjects with MLEs had significantly more non-psychotic psychiatric disorders as well as hospital treatment for these disorders than either controls or subjects with PLEs. However, further analyses showed that this was explained by having more lifetime psychiatric disorders already at the baseline assessment.

Since hypomanic personality has previously been found to predict psychiatric disorders in young adult samples (Kwapil et al. 2000; Miettunen et al. 2011), it is of interest that baseline MLEs did not predict bipolar disorder or other severe mental disorders in this study. However, the sample size of the study groups was relatively small considering the incidence rates of psychotic disorders, particularly in the age group of the present study. Thus, it is possible that with larger study samples the results could have been different.

There have been studies about the relationship between bipolar disorder and borderline personality disorder (Antoniadis et al. 2012), and it has been found that there is some overlap in self-reported symptoms of bipolar disorder and borderline personality disorder, as well as some overlap in phenomenological and neurobiological features of these disorders (Baryshnikov et al. 2015). Whether MLEs reported in the CIDI reflect bipolar disorder susceptibility or more broadly unspecific affective instability without pronounced psychotic susceptibility remains open. Even though the subjects with MLEs did not have a diagnosis of bipolar disorder or borderline personality disorder at baseline, it may be that some of them share similar subthreshold features or vulnerability, possibly predisposing them to some future psychiatric condition or having a relapse to the same condition as before. Previously it has been found that subthreshold affective symptoms and substance use disorders in young subjects might predict bipolar disorder (Ratheesh et al. 2015b). However, studies are few and no established tools to identify individuals at risk for developing bipolar disorder have yet been developed (Bechdolf et al. 2014).

The subject with PLEs did not differ from the controls in the prevalence of psychiatric disorders during follow-up. None of the subjects with PLEs had psychosis during the follow-up, suggesting that PLEs in middle-aged subjects

may not predict future psychosis. Even though psychotic experiences mostly have onset in adolescence or young adulthood, there are subjects with late onset psychotic experiences (McGrath et al. 2016). Werbeloff et al. (2012) followed a cohort of young subjects for 24 years and found that PLEs predicted a risk for later hospitalization for non-affective psychosis, but mostly during the first five years after baseline. Because their study subjects were relatively young (mean age at baseline 29.4), the possibility of a lengthy prodromal period could not be ruled out. Still, their study found a transition rate at around 1% during the first 5 years (Werbeloff et al. 2012). In our study, the subjects were significantly older at baseline, with a mean age of 49.5 years in the PLE group, 46.8 years in the MLE group and 50.6 years in the control group, so most likely there were no subjects with prodromal symptoms. In a study by Werbeloff and colleagues (2012), the cumulative incidence of later psychotic hospitalization associated with attenuated psychotic symptoms was higher in respondents with poor social functioning at baseline. Moreover, impaired social functioning has been found to be a risk factor for future schizophrenia (Krabbendam et al. 2004). The subjects with PLEs reported slightly poorer current psychosocial functioning levels than controls at baseline (assessed with the GAF), but they might not have been as severe as with subjects who later developed psychosis (Sparks et al. 2010).

Neuropsychological performance at baseline did not associate with later psychiatric disorders in subjects with PLEs or MLEs. Neuropsychological deficits have previously been found to predict psychosis in adolescents and young adults in Clinical High Risk (CHR) samples (Keefe et al, 2006; Wood et al, 2007) as well as in subjects with a family history of schizophrenia (Erlenmeyer-Kimling et al, 2000). Keefe et al. (2006) found that those CHR subjects who progressed to psychosis had more severe deficits, while other at-risk subjects did not differ significantly from controls in neuropsychological performance. In studies on the associations of cognitive functions and future bipolar disorder, lower visuospatial functions and higher arithmetic functions at age 20 have been found to associate with greater odds for later bipolar disorder in male conscripts (Tiihonen et al. 2005). In other studies, young subjects who later developed bipolar disorder have been found not to differ from controls (Reichenberg et al. 2002; Reichenberg et al. 2002; Zammit et al. 2004) or even have above average cognitive functioning (MacCabe et al. 2013).

Better performance in some of the verbal memory measures at baseline was associated with lower likelihood for later psychiatric disorders in the controls. Previously, better performance in verbal memory measures has been associated with lower likelihood of later psychiatric disorder in general population studies (Gale et al. 2011) and in cohort studies (Martin et al. 2007).

In conclusion, the results suggest that MLEs and PLEs are not effective predictors of severe psychiatric disorders beyond young adulthood. However, future studies with larger study groups are warranted.

5.5 Methodological considerations

All participants of the present thesis were drawn from the Finnish population, and they were assessed applying systematic methodological and diagnostic procedures. Healthy siblings of the schizophrenia patients, subjects with PLEs and MLEs and the control subjects included in the studies were without current mental or substance use disorders, diminishing the potentially confounding effect of other conditions on neuropsychological assessment. The neuropsychological assessment and psychiatric evaluation were done in a systematic manner for all subjects. In addition, control subjects in the study were a representative sample from the Finnish population. Because psychiatric symptoms and mild psychiatric disorders are relatively common in the general population, the controls with a lifetime, non-psychotic Axis I disorders were included, while those with a current disorder were excluded. This was done in order to avoid selection of an atypical, “super-normal”, control sample.

Statistical methods used for Studies I and II including family data were adjusted for family correlation. The modifying effects of demographic variables such as age, gender and education were controlled for in all of the analyses. Moreover, most subjects in the schizophrenia family data were over the mean risk age for conversion to schizophrenia, which is below 40 years of age (Franke et al. 1994). This made it less likely that the non-psychotic disorders in the sibling group would turn into psychosis or that the neuropsychological deficits found would have been related to the prodromal period preceding psychosis. The PLE and MLE subjects in Studies III and IV were also middle-aged, making it possible to study potential risk symptoms for psychotic disorders in an age group scarcely previously studied.

There are several methodological limitations. Studies I and II represent neuropsychological functioning in familial schizophrenia. Thus, our results may not be generalizable, as such, to all situations. The neuropsychological test battery that was used in all of the Studies could have been more thorough with the inclusion of measures for social cognition, visual reasoning and visual memory. Also, it is possible that if more demanding measures of memory, attention and executive functioning had been used it could have revealed more differences between groups. The CVLT, which has been widely used in research on cognition in psychotic disorders, was also used as a measure of verbal learning and memory in this study. Although its use allows comparison with international studies, the test has not been validated in

Finnish. This can be considered as a limitation to the present study. In Study II, a more effective or up-to-date assessment method of anhedonia, other than the Chapman scales, with a method for differentiating consummatory and anticipatory or remembered pleasure, might have yielded additional information on the relationship between neuropsychological performance and anhedonia. In Studies III and IV the decision not to use Bonferroni correction was made because diminishing power in already low power analyses (small sample sizes) might have increased the risk of not detecting a true difference. The Bonferroni correction has been criticized for causing loss of power to detect real effects (Glickman, 2014), which influenced the decision not to perform Bonferroni adjustment. Considering the relatively small sample sizes in all of the present studies, generalizability may be limited, and further research is needed to confirm these findings.

In Studies III and IV, the focus was on subjects with PLEs or MLEs, derived from the CIDI, who also went through a thorough diagnostic procedure of the Psychosis in Finland of the Health 2000 Study with no observed diagnoses for a psychotic disorder. Because PLEs and MLEs are defined as subthreshold symptoms, and the CIDI is designed as a diagnostic tool for mental disorders, it can be argued that our subjects with PLEs and MLEs do have relatively noticeable subthreshold psychotic experiences. However, the CIDI has been criticized for not being sensitive enough, being able to detect only 26.6% of subjects with a psychotic disorder and 25% of those with bipolar disorder (Perälä et al. 2007). Therefore, even though the CIDI may be considered to have been rather strict on one hand, one might question whether more subjects with PLEs or MLEs could have been found with a different methodology. Adding another measure for PLEs and MLEs would have made comparison of methodology possible and added reliability.

5.6 General discussion and conclusions

Different aspects of the relationship between cognitive performance and susceptibility to psychosis were explored in Studies I-IV where the focus was on less-studied middle-aged subjects, instead of adolescents/young adults who have been studied more often. According to the results of the study, healthy siblings of schizophrenia patients seemed to have mild but recognizable deficits in neuropsychological performance in comparison to population controls, even when the siblings with non-psychotic disorders are excluded (Study I). Elevated physical anhedonia related to poorer performance on some measures of verbal function, but the effect was separate from the effect of familial liability on cognition (Study II). The detected cognitive deficits were mild and most likely to not severely interfere with daily life, considering that people in general have marked heterogeneity

in their cognitive profile and performance. However, considering that the education level of the siblings was closer to that of affected subjects than to that of controls, it is possible that these deficits, although mild, might have affected the achieved education level or educational demands of professions selected within this group. Unfortunately, these aspects were not explored further and should be studied in future.

Middle-aged subjects with psychotic-like or manic-like experiences, assessed with relatively strict criteria, did not differ significantly from control subjects regarding cognitive functioning. Most interestingly, the subjects with PLEs were more similar to controls in psychosocial and occupational functioning than subjects with MLEs (Study III). Subjects with MLEs had more lifetime psychiatric disorders and also differed from controls in interpersonal, but not occupational, functioning, suggesting that despite a good enough performance in professional life there may be some form of psychological fragility present in these subjects. In this age group, neither PLEs nor MLEs predicted future psychosis in an 11-year follow-up (Study IV), suggesting that in middle-aged persons these symptoms may be more benign regarding risk for conversion to psychosis than in younger people. In the future, investigating larger samples with PLEs and MLEs with a broader methodological perspective, including personality assessment, would be recommended.

5.7 Implications for clinical practice and future research

This thesis focused on adult subjects who presumably had a more pronounced risk for psychotic disorders than a general population without familial or clinical risk features. In general, these middle-aged subjects seemed to differ from younger at-risk (whether clinical or familial) subjects.

Relatives of schizophrenia patients have neuropsychological deficits that are milder than those of affected subjects. In familial schizophrenia, these neuropsychological deficits seem to be related partly to familial vulnerability as well as to the shared genetic features among family members, even though with affected subjects the deficits are more severe. In clinical practice, it is important to notice that middle-aged, or older, mentally healthy relatives of schizophrenia patients may have mild neuropsychological impairment, in order to be able to interpret findings correctly when assessing cognitive function of such persons for reasons such as a suspected neurological condition.

In non-psychotic subjects from schizophrenia families, physical and social anhedonia levels were not different from those of population controls. This may suggest that elevated anhedonia is more specifically related to the illness itself than familial vulnerability, and therefore should in clinical settings be

taken seriously. Studies that use different measures of anhedonia than self-report scales may offer new insight into the phenomenon of negative symptoms of schizophrenia.

PLEs are a part of clinical vulnerability to psychosis and, in CHR settings (adolescents and young adults), are known to be associated with the prodromal period that anticipates the onset of psychosis. In CHR settings they also associate with neuropsychological deficits. PLEs are relatively common in the general population with prevalence of about 7% (Linscott and van Os, 2013). In middle-aged subjects from a general population survey, the subjects with PLEs did not differ from population controls in any assessed cognitive function, nor in incidental non-psychotic psychiatric disorders. PLEs or MLEs did not predict conversion to psychosis during 11-year follow-up in middle-aged adults.

It may be that in non-help-seeking middle-aged subjects these experiences are of a benign nature. Since cognitive functioning of subjects with PLEs did not differ from that of controls, it may also be that sufficient cognitive functioning might have protected against full manifestation of psychosis. In general, the study suggests that in middle-aged subjects who have no history of a psychotic disorder, the presence of PLEs does not seem to represent susceptibility to psychosis, nor to non-psychotic psychiatric disorders. This does not imply, however, that disturbing PLEs should not be taken seriously in clinical practice.

Even though manic-like experiences did not predict a psychotic disorder during the 11-year follow-up, it should be noted that in comparison to controls and subjects with PLEs the subjects with MLEs had several distress-related findings at baseline and more non-psychotic psychiatric disorders, deaths and dropouts during follow-up than other subjects (also those with PLEs). Clinically, MLEs or other symptoms suggestive of affective instability should be taken seriously and possible supportive or treatment options should be carefully considered. If a patient manifests PLEs or MLEs as well as compromised neuropsychological performance, thorough clinical evaluation of the situation is warranted.

In future research, a long-term follow-up period would add to our knowledge of susceptibility to psychosis and other mental disorders in middle-aged populations with different vulnerability features. Of particular interest would be to study the aging process of the siblings' group with reassessment of neuropsychological and psychiatric measures. A possible predictive value of neuropsychological impairment at baseline in this population might manifest itself.

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